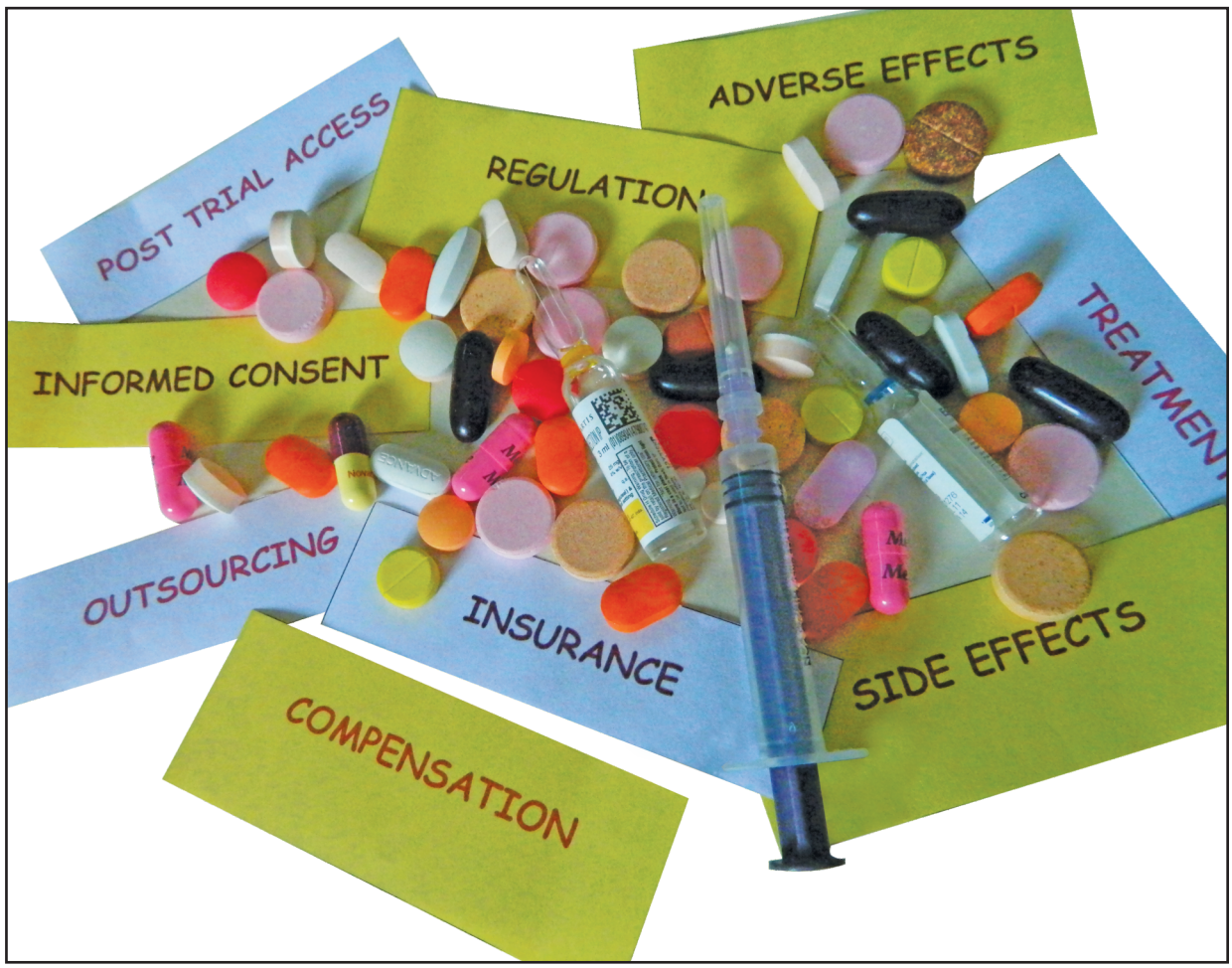
Exploratory Study on Clinical Trials Conducted by Swiss Pharmaceutical Companies in India:

Issues, Concerns and Challenges



BD
Berne Declaration
Déclaration de Berne
Erklärung von Bern

Sama

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The Berne Declaration

Founded in 1968, the Berne Declaration (BD) is an independent Swiss non-governmental organisation formed to combat the root causes of poverty by promoting more equitable and sustainable relations between Switzerland and the developing world. As a not-for-profit organisation with 23 500 members, the BD is committed to global justice and addresses issues of trade policy, commodity production and trade, the politics of food, finance, fair trade and health. As part of a worldwide network of human rights groups, environmental and development organisations, the BD promotes a more equitable and humane route to global development. To this end, the BD carries out investigative research, runs public campaigns to raise awareness and undertakes successful advocacy work in Switzerland and on the international stage.

More information on www.ladb.ch

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Sama – Resource Group for Women and Health

Sama is a Delhi-based non governmental organisation working on issues of women's health and rights. Sama seeks to locate the concerns of women's health in the context of socio-historical, economic and political realities, and find linkages between women's well-being and livelihoods, food, violence and other larger issues that affect their lives. Sama's core work areas include issues related to Public Health, Reproductive and Medical Technologies, Ethics and Regulations of Clinical Trials and Violence Against Women. Sama engages with a range of organisations, health networks, people's health movement, policy makers and academia through strategies of policy monitoring and advocacy, capacity building, research, knowledge creation and dissemination.

More information on www.samawomenshealth.org

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Report available on www.ladb.ch or upon request at info@ladb.ch, or sama.womenshealth@gmail.com

Contents

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Errors and omissions, if and when they occur, are all ours.

For strategic reasons and to maximise profits, industry-sponsored clinical drug trials on human participants are increasingly offshored in developing and emerging countries. In those countries, pharmaceutical companies can find a large pool of vulnerable people willing to take part in drug trials as it represents often their only treatment option. In addition, weak regulatory environments enable the pharmaceutical multinationals to shorten clinical trials duration. This increases significantly the risk of ethical violations. Concerned about this situation, the Berne Declaration launched several investigations in 2012 and 2013. Four field studies took place in Argentina, India, Russia and Ukraine to better understand these contexts in which numerous clinical trials take place. How is the regulatory system performing? Are the ethical standards respected? How do Swiss firms conducting clinical trials behave in these countries? A research was also carried out in Switzerland to understand how Swissmedic – the Swiss medicines agency – functions and carries out the ethical control of clinical trials that were conducted in third countries. The field studies were done by investigative journalists and by an NGO specialised in the field. The five reports are available on www.ladb.ch or upon request at info@ladb.ch.

This report is based on the research done in **India** by **Sama**, an NGO working on the regulation of clinical trials.

Abbreviations

AE	Adverse Event
BD	Berne Declaration
CRC	Clinical Research Coordinator
CDSCO	Central Drugs Standards and Control Organisation
CRO	Contract Research Organisation
CTRI	Clinical Trial Registry of India
CoI	Conflict of Interest
CIOMS	Council for International Organisations of Medical Sciences
DCA	Drugs and Cosmetics Act
DCGI	Drug Controller General of India
DoH	Declaration of Helsinki
EC	Ethics Committee
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
HPV	Human Papilloma Virus
HoD	Head of Department
ICMR	Indian Council of Medical Research
ICH	International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IP	Intellectual Property
IRB	Institutional Review Board
ICF	Informed Consent Form
IEC	Institutional Ethics Committee
IPD	Indoor Patient Department
IPAB	Intellectual Property Appellate Board
KI	Key Informant
OPD	Outdoor Patient Department

MoHFW	Ministry of Health and Family Welfare
MP	Member of Parliament
MCI	Medical Council of India
PI	Principal Investigator
PIL	Public Interest Litigation
PTA	Post-Trial Access
R&D	Research and Development
RTI	Right to Information
SMO	Site Management Organisation
SAE	Serious Adverse Event
SoP	Standard Operating Procedures
TRIPS	Trade-Related Aspects of Intellectual Property Rights
CTP	Clinical Trial Participant
US	United States of America
WHO	World Health Organisation
WTO	World Trade Organisation
WMA	World Medical Association

1

Context

1.1. The Clinical Trial Sector in the Pharmaceutical Industry

India's pharmaceutical industry is globally renowned for its traditional strengths in manufacturing, including contract manufacturing of drugs. India's domestic drug market is the 14th largest in the world,[1] but is perceived by the global pharmaceutical market as having huge potential. India is known as the pharmacy of the developing world, with one of the world's largest industry providing generic, low-cost medicines to developing and least developed countries. This recognition of India's pharmaceutical industry is in the context of substantive shifts currently taking place: from a manufacturing location preferred by multinational drug manufacturers towards its emergence as a location of choice for a wide range of outsourcing deals, partnership initiatives, and other contractual arrangements that enable the creation of vast networks, of which India is expected to be an important part.[2] This shift is largely the consequence of the high costs of research and development (R&D) and administration in countries such as the United States that so far have served as the preferred trial sites and have been regarded as natural choices by the pharmaceutical industry.

Increasingly, drug manufacturers are moving their research and clinical trial activities to the subcontinent to capitalise on India's high levels of scientific expertise, low costs, huge patient population, genetic diversity, information technology infrastructure, and TRIPS-compliant Intellectual Property Rights (IPR) environment, which make it an ideal site for conducting clinical trials.

India offers substantial advantages in terms of cost efficiency: the cost of conducting a trial here is less than half the cost in the United States.[3] The Indian Patent Act and the amendments to the Drugs and Cosmetics Act (DCA) in 2005[4] have provided significant impetus to the growth and development of the clinical trial industry in India.

According to the World Health Organisation's (WHO) International Clinical Trials Registry Platform, 6,049 trials were registered in India on 14 June 2013.[5] About 2 per cent, that is, fewer

than 2,000, of the 118,804 human trials registered in 2013 the world over are being conducted in India, as compared to about 8 per cent (9,352 trials) being conducted in China.[6]

The growing clinical trial industry in India comprises pharmaceutical companies, CROs,[7] data-processing centres, recruiters, and affiliated private and public hospitals and clinics. While the large majority of the trials are coordinated by the pharmaceutical companies themselves, several of the trials are also outsourced to clinical/contract research organisations. Contract research in the Indian pharmaceutical industry is already robust, and was estimated by the Chemical Pharmaceutical Generic Association to be worth between USD100 and USD120 million in 2005, while growing at a rate of 20 to 25 per cent per year. The CRO market is currently worth USD0.3 billion, projected to reach USD1 billion by 2014.[8] The leading players in India include Clinigene International, Vimta Labs Ltd, and Lotus Labs, besides multinationals such as Quintiles, Pharmanet, SIRO Clinpharm, and Clintec.[9]

Unlike the United States, where CROs are codified in a Federal Register, in India, Schedule Y of the DCA, for the regulation of clinical trials,[10] does not make any mention of them, let alone lay down clauses for their regulation.

1.2. Swiss Pharmaceutical Companies in India

The pharmaceutical/health care industry has always featured as an important sector in Swiss–India trade, one perceived as possessing huge potential for collaboration and an expanding market share.[11] Hence, pharmaceuticals feature among the major export items from Switzerland to India.[12] In general, India is also seen to offer significant business potential because of its large and expanding domestic market, with the pharmaceutical sector featuring prominently in the projected scenario. There are about 180 joint ventures or wholly owned subsidiaries of Swiss companies operating in India, and they have established collaborations with other companies in the pharmaceutical sector in India, thereby continuing to maintain themselves among the top-ranking firms.[13]

Swiss pharmaceutical companies Roche (No. 3 in 2012) and Novartis (No. 2) are among those systematically investing the most in R&D worldwide throughout all industry sectors, according to an annual rating by Booz & Co.[14]

For example, Novartis AG has a 76.42 per cent stake (as on 30 September 2012) in Novartis India, up from 50.9 per cent. Novartis has two wholly owned companies in India—Novartis Consumer Health Private Limited and Sandoz India Private Limited. Novartis India also features among the top selling pharmaceutical companies in India, according to the Bombay Stock Exchange listings,[15] although its stock has dropped following the recent landmark judgement in the Glivec case, as has that of other multinational pharmaceutical companies.

Nevertheless, Novartis was recently asked to check certain malpractices such as the bribing of stockists, for over a year, with massive discounts and freebies, to push sales of Galvus, a leading anti-diabetes drug.[16]

Although the pharmaceutical industry has always been a fairly well-established part of Swiss-India collaboration and trade, the emergence of India as a location for clinical trials by Swiss pharmaceutical companies is more recent. Swiss pharmaceutical giants such as Novartis and Hoffman-La Roche have established, and increased their stakes in, subsidiary companies in India to take advantage of opportunities there.

Patent litigations

Since the introduction of a product patent regime in 2005, Swiss companies have filed for several patents for pharmaceutical products in India. Novartis and Roche have been in the news more recently for their involvement in patent disputes/claims regarding drug innovation and novelty.

Indian patent laws have set a high threshold for the patenting of new versions of existing drugs, demanding that the modified compounds must show improved efficacy. Legal judgments in India have set a critical precedent for ensuring access to medicines for not only Indians but also for people in the developing world.

While the patent applications have been rejected or the patents have been revoked, Swiss pharmaceutical companies continue to price their drugs at highly unaffordable rates. The Novartis case in India focused the debate on the fact that the patent office should make a careful decision in distinguishing between what should be allowed to be patented and what should not.

Despite the hype that Novartis has created around the rejection of one patent application, Swiss companies did indeed receive patent protection for several drugs. However, what has been downplayed is the fact that the companies have also priced their patented medicines in a manner that makes it very difficult for poor patients to access them, thus denying them affordable treatment and medicines. This also makes it difficult for patient groups to advocate that the government should provide treatment.

Case Study 1

Glivec, a cancer drug, has been patented in 40 countries, but its application for similar protection in India was rejected in 2006, as the patent office ruled that the active ingredient, imatinib mesylate, was a known compound before Glivec was developed, and was therefore ineligible. The Novartis case was one of the first cases after the amendment to the Patents Act, 2005, to be examined, opposed, and rejected by the Indian patent office. Novartis' patent application was rejected on several grounds, including Section 3(d), which prevents the granting of patents on a new form of a known substance unless it differs significantly in efficacy. This tougher patentability standard was challenged by the Swiss company Novartis in the Supreme Court of India. In April 2013, the Supreme Court dismissed Novartis' attempt to win patent protection for Glivec. The ruling benefitted not only cancer patients suffering from chronic myeloid leukaemia but also Indian drug manufacturers like Cipla Ltd. and NatcoPharma Ltd., which were already selling generic versions of the drug in India at around one-tenth the price being charged by Novartis. The ruling has provided leverage to the local companies that act as major suppliers of inexpensive generics to India's rapidly growing USD13 billion-a-year drugs market and also to companies from across the developing world.[17]

Case Study 2

In May 2013, a division bench of the Madras High Court, in the state of Tamil Nadu in India, dismissed the appeal of Hoffman-La Roche against Gujarat-based pharmaceutical company Intas Biopharmaceuticals for selling Erlotib, the generic version of the former's patented drug Tarceva, in Tamil Nadu.[18] The former had alleged violation of patent rights for Tarceva (erlotinib hydrochloride), a drug for the treatment of non-small cell lung cancer.

This litigation is one of several such cases between Roche and Indian companies, including Cipla Ltd, Natco Pharma Ltd., and Intas Biopharmaceuticals, in connection with this drug. On 3 March 2006, Roche proudly announced that it would be the first pharmaceutical company in India to receive a product patent under the new patent regime for peginterferon alfa-2a (sold by Roche under the brand name Pegasys), used in the treatment of hepatitis C. The official distributors of Roche in India priced one 180 mcg vial of Pegasys at USD247 (INR13,700). India, with its growing hepatitis C epidemic, is a lucrative market for Roche, but this price made it very difficult for people living with HIV to convince the Department of AIDS Control to treat patients co-infected with HIV and HCV. Finally, after a six-year-long battle, the Intellectual Property Appellate Board (IPAB), based in Chennai, revoked the patent granted to Roche for pegylated interferon alfa-2a. The alleged invention (interferon alpha-2a + polyethyleneglycol) was held to be obvious.

Case Study 3

Roche was granted a patent in 2007 for its oncology blockbuster drug Herceptin, also known as trastuzumab, used for the treatment of breast cancer. Filed in 2000, the patent is valid until 2020. The patent has been opposed since the beginning as it had been "granted in violation of the provisions of the Indian Patent Act and stands on very shaky legal ground. A post-grant opposition to this patent has been pending with the Kolkata Patent Office for more than five years".[19] In August 2013, the latter Patent Office announced that they had partly revoked patents granted to Roche for Herceptin. Soon after, Roche announced that it had relinquished its patent for its breast-cancer drug, trastuzumab (Herceptin) in India. The decision of Roche should "not be mistaken for altruism – it is a face-saving gesture in response to the eroding legitimacy of both the patent and the pricing policy in India". [20] Herceptin is currently priced at USD15,000–USD17,000 (INR 6–8 lakhs) for a full course of 12 injections, and therefore unaffordable by most people who require the drug for their treatment. It was also under the threat of a compulsory licensing, which suggests that Roche's decision to relinquish its patent was "a tactical move to avoid compulsory licensing, which would have more serious and far-reaching implications for its plans in the Indian market". [21]

Swiss companies are also opposed to domestic regulation and price control of medicines sold in the Indian domestic market, and more recently, the Indian government's attempts at regulating clinical trials, because multinational pharmaceutical companies continue to outsource them to India to save on drug development costs.

1.3. Study Rationale

As the pace, scope, and scale of international collaborative biomedical research have increased over the past decade, ethical concerns with regard to the design, conduct, and follow-up of international trials have resurfaced. The debates over the conduct of clinical trials by CROs, research institutions, the pharmaceutical industry, international health non-governmental organisations (NGOs), and the state, are revealing. Many Indian sites for clinical trials and research lack affiliation with any independent institutions that will monitor and audit the drug trials. Furthermore, many clinical trials are conducted by private clinics and research centres in non-compliance both with Schedule Y of the DCA and the regulations of the CDSCO. Sponsors, too, recruit private practitioners in clinical trials as investigators, which is one of the reasons for the increasing number of clinical trials in India. Sites where clinical trials are held are also shifting from the teaching hospitals of academic and research institutions to the offices of private physicians and CROs. This shift into the private sphere raises doubts about the veracity of not only the manner in which the clinical trials are conducted, but also the outcomes, which could be manipulated to suit the results desired by the sponsor.

In India, the current infrastructure for regulation, ethics review and monitoring is insufficient to regulate clinical trials (ref: Sama material, HPV enquiry committee report, Sama-led National Consultation held in October 2011, any other critical commentaries). For example, several media articles and RTI (Right to Information) inquiries have pointed to the fact that an obvious conflict of interest exists in the case of doctors receiving benefits from the trial sponsors. "Doctors conducting trials also receive commissions per patient recruited, creating an incentive to enrol more people in the trials. This leads to a violation of the physician–patient relationship of trust."[22]

Similarly, the recent investigation undertaken by the Department-related Standing Committee on Health and Family Welfare, whose report "Functioning of the Central Drugs Standard Control Organisation (CDSCO)" was presented before the Rajya Sabha on 8 May 2012, and provided authoritative, clear, and detailed evidence of a severely flawed drug regulation system. The mandate of this system evidently was "to meet the aspirations . . . demands and requirements of the pharmaceutical industry". The names of some Swiss pharmaceutical companies also featured in the report.

In the case of four drugs (10%) (Everolimus (Novartis); Buclizine (UCB); Pemetrexed (Eli Lilly); and Pregabalin (FDC)), not only were the mandatory Phase III clinical trials not conducted but not even the opinion of experts was sought. The decision to approve these drugs was taken solely by the non-medical staff of CDSCO.

In the case of two drugs (Dronedarone (Sanofi) and Aliskiren (Novartis), clinical trials were conducted on just 21 and 46 patients respectively as against the statutory requirement of at least 100 patients.

Source: *Department-related Parliamentary Standing Committee on Health and Family Welfare,Fifty-ninth Report on the Functioning of the Central Drugs Standard Control Organisation (CDSCO), May 2012.*[23]

The findings of the Parliamentary Standing Committee,[24] endorsed by Members of Parliament (MPs) from all political parties, are wide-ranging: severe shortages of qualified staff and other resources; poor data collection and maintenance; grossly insufficient monitoring of industry compliance with regulatory requirements; incomplete, missing, or 'untraceable' files; flaws in the DCA and the Drugs and Magic Remedies Act 1954 and in their implementation; bypassing of regulatory requirements in the interests of industry, including granting marketing approval to dozens of drugs without the mandatory Phase III clinical trials in the guise of "the public interest"; approval of dangerous and irrational drugs; improper and unethical testing practices; a nexus between regulators, medical experts, and industry, etc. In general, it notes that "irregular approvals spare drug producers the cost and efforts but put Indian patients at risk."

Subsequently, the issues were raised once again in the Sixty-Sixth Report on Action Taken by the Government on the Recommendations/ Observations Contained in the Fifty-Ninth Report on the Functioning of CDSCO.

In light of the current context, a closer look at ongoing clinical trials in India is required. The observation and documentation of practices should be extremely timely and meticulous, as these are important steps in providing input for the preparation of policies and guidelines for pharmaceutical research, production, and distribution, as well as for processes that ensure the ethical conduct of trials.

In the case of 11 drugs (28%), Phase III clinical trials mandated by the Rules were not conducted. These drugs are i. Everolimus (Novartis), ii. Colistimethate (Cipla), iii. Exemestane (Pharmacia), iv. Buclizine (UCB), v. Pemetrexed (Eli Lilly), vi. Aliskiren (Novartis), vii. Pentosan (West Coast), viii. Ambrisentan (GlaxoSmithKline), ix. Ademetionine (Akums), x. Pirfenidone (Cipla), and xi. Pregabalin by FDC, Methylcobolamine, Alpha Lipoic Acid, Pyridoxine and Folic Acid (Theon).

Source: *Department-related Parliamentary Standing Committee on Health and Family Welfare, Sixty Sixth Report on Action Taken by the Government on the Recommendations /Observations Contained in the Fifty Ninth Report on the Functioning of (CDSCO), April 2013.*[25]

So when BD approached Sama with a proposal to look into the clinical trial industry in India, Sama agreed to document the conduct of clinical trials sponsored by Swiss pharmaceutical companies in India and to verify whether these companies comply with the relevant ethical standards.

2

Clinical Trials in India: the Legal, Regulatory and Ethical Environment

India's clinical trial sector, which was dubbed a 'sunshine sector' and is perceived as a sector with high potential, nevertheless faces several challenges, including the lack of a standardised regulatory system and significant delays in receiving approvals. Given the quick growth in the number of clinical trials conducted in India, legal and ethical issues relating to these trials have become increasingly complex, as the law is still in a nascent stage of development.

2.1. Drugs and Cosmetics Act, 1940

The term "clinical trial" was been defined in the Drugs and Cosmetics Act, 1940, and the Drugs and Cosmetics Rules, 1945. It refers to a systematic study of new drug(s) in human subject(s) for the purpose of generating data for discovering and/or verifying the clinical, pharmacological, and/or adverse effects of the new drug(s) with the objective of determining its safety and/or efficacy.

The rules and regulations relating to clinical trials are laid down in Schedule Y of the DCA. To conduct medical trials in India, approval from the Drug Controller General of India (DCGI) is mandatory. The companies, sponsors, and funders conducting clinical trials have to comply with all the requirements for registration as provided by the guidelines for "Pharmaceuticals for Human Use", "International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)", and "Good Clinical Practices (GCP)". The DCGI categorises clinical trials into two types. Type A trials are those trials for which the study protocol has been approved by an authorised regulatory body in one or more developed countries. Such trials are approved using a fast-track mechanism. Type B trials comprise all those trials that do not fall under Type A. It takes longer to get approvals for these trials.

Schedule Y of the DCA lays down the basic requirements and stages for the conduct of clinical trials; lists the documents to be submitted; describes the responsibility of the (i) sponsors, (ii) investigators, and (iii) ECs; and addresses the subjects of informed consent, the types of studies to be undertaken, the structure of the reports to be submitted, the procedure for the reporting of AEs, SAEs, death, etc.

Under the DCA, preparing and implementing regulations for the sale, manufacture, and distribution of drugs is primarily the concern of the state authorities. The central authority, that is, the CDSCO, is responsible for approving new drugs and clinical trials, introducing quality control standards, co-ordinating the activities of the State Drug Control Organisations, and providing expert advice to ensure uniform implementation of the provisions of the DCA. To further strengthen the regulatory provisions and the monitoring mechanisms of clinical trials, the Drugs and Cosmetics Rules, 1945, have been amended as follows:[26]

1. Amendment vide Gazette Notification G.S.R. 53(E) dated 30 January 2013 specifying the procedures for analysing reports of SAEs that occur during clinical trials and the procedures for the payment of compensation in the case of trial-related injury or death as per the prescribed timelines.
2. Amendment vide Gazette Notification G.S.R. 63(E) dated 1 February 2013 specifying various conditions for the conduct of clinical trials, the authority for conducting clinical trial inspections, and the actions in case of non-compliance.
3. Amendment vide Gazette Notification G.S.R. 72(E) dated 8 February 2013 establishing the requirements and guidelines for the registration of the Ethics Committee.

2.2. Ethical Guidelines in India

The Indian Council of Medical Research (ICMR) is the apex body that regulates clinical trials. The ICMR issued the "Policy Statement on Ethical Considerations Involved in Research on Human Subjects" in 1980, subsequently revised in 2000 and renamed "Ethical Guidelines for Biomedical Research on Human Subjects". These ethical guidelines require that clinical trials be conducted in accordance with the principles and guidelines laid down in the Council for International Organisations of Medical Sciences (CIOMS), the Declaration of Helsinki and the Universal Declaration on Bioethics and Human Rights (2005). Clinical trials have to follow the principles of essentiality, voluntariness and informed consent, non-exploitation, privacy and confidentiality, precautions and risk management, professional competence, accountability and transparency, maximisation of public interest and distributive justice, institutional arrangements, public domain, totality of responsibility, and compliance. However, the ICMR Ethical Guidelines do not have statutory status or legislative power.[27] The Biomedical Research on Human Participants (Ethical, Legal, and Social Issues) Bill, 2010, sponsored by ICMR, is still in the pipeline.

The Medical Council of India (MCI) Act, 1956, and the Central Council of Indian Medicine Act, 1970, also regulate the conduct of clinical trials.[28]

2.3. Indian GCP Guidelines

In December 2001, an expert committee was set up by CDSCO in consultation with clinical experts to formulate the GCP guidelines for the Drug Technical Advisory Board (DTAB), the highest technical body under the DCA. It has also endorsed the adoption of the GCP guidelines for streamlining the conduct of clinical studies in India. These guidelines have been developed in line with the ICH, USFDA, and European GCP guidelines, as well as the Ethical Guidelines for Biomedical Research on Human Subjects issued by the ICMR.[29]

The implementation of the relevant laws and policies is a matter of grave concern even as we formulate a comprehensive legal framework for the conduct of clinical trials in India. How accessible will these legal provisions be for clinical trial participants? Will clinical trial participants have the ability, capacity, and opportunity to make use of these provisions in safeguarding their interests?

3

Methods

This report is based on the findings of a study conducted in India in the period July 2012–May 2013. We employed qualitative research methods to explore the conduct of clinical trials sponsored by Swiss pharmaceutical companies and to verify if these companies comply with the relevant ethical standards and with the regulatory environment in India from the perspectives of various constituencies and stakeholders. These included clinical trial participants (CTPs)[30] and other key informants (KIs)[31] such as principal investigators (PIs), clinical research coordinators (CRCs),[32] and representatives of contract research organisations (CROs). The study specifically looked at aspects and procedures related to the recruitment process, the securing of informed consent, the reporting of serious adverse events (SAE), post-trial access (PTA), insurance, and compensation. A critical analysis of the relevant bills, laws, and guidelines was also undertaken to gain an understanding of the status of the relevant legislation, the regulations and policies that affect the clinical trial industry, and the reports produced by the Parliamentary Committee to identify the issues needing public debate and discussion.

3.1. Study Sites

3.1.1. Web search

An extensive search was conducted through two trial registries—clinicaltrials.gov (a US-based registry)[33] and the Clinical Trial Registry of India (CTRI)[34]—using keywords such as the names of Swiss companies in conjunction with the name of the relevant Indian city/state. This exercise provided lists of institutions—hospitals (both private and public), medical colleges, nursing homes, clinics, research institutes, CROs—that were conducting trials sponsored by Swiss pharmaceutical companies across the country.

3.1.2. Selection of states

Since the objective of the study was to develop an in-depth understanding of the establishment and escalation of clinical trials in India by global pharmaceutical companies, particularly

Swiss companies, the extent and stage of the growth and expansion of clinical trials in certain states was an important feature that was considered while choosing the sites.

Sama selected six Indian states: Gujarat and Maharashtra (western region); Delhi, Rajasthan, and Uttar Pradesh (northern region); and Andhra Pradesh (southern region). Delhi, Maharashtra, Gujarat, and Andhra Pradesh were selected because a large number of clinical trials are conducted in these states, that is, 3,754 registered under the Clinical Trial Registry of India (CTRI), as per the 2011 data. The number of clinical trials conducted by Swiss pharmaceutical companies was also higher in these states, particularly in Andhra Pradesh and Gujarat, which have the highest number. Although the number of clinical trials conducted by Swiss pharmaceutical companies was not as high in Rajasthan and Uttar Pradesh as the other mapped states, they were easily accessible to the study team. In addition, these sites were better equipped with local investigators.

3.2. Sampling

3.2.1. Selection of the clinical trial sites

On the basis of the research findings, we have observed the following:

1. Most of the trials registered in these states were Phase III, and very few were Phases II and IV.
2. Most of these trials were on certain drugs for cancer, metabolic disorders (diabetes), respiratory tract infections, mental disorder, psoriasis, and cardiovascular disease, such as Aliskiren, Bevacizumab, LCZ696, Iloperidone, Safinamide, DEB025, Enalapril, Canakinumab, Imatinib mesylate, QAW039, Erlotinib, Amlodipine, and Secukinumab.

An initial search of the trial registries – as described in 3.1.1. Web search, above – was undertaken prior to the fieldwork to identify the sites that were conducting drug trials for Swiss pharmaceutical companies, such as Novartis and Roche, across various therapeutic areas in these six states.

3.2.2. Selection of Key Informants and Clinical Trial Participants

The determination of the sample size was dependent on the availability of, and access to, the KIs and the CTPs.

Based on the list, the study team contacted 135 institutions across the above-mentioned six states (Gujarat–28; Maharashtra–30; Andhra Pradesh–30; Uttar Pradesh–10; Rajasthan–12; and Delhi–25). Of these 135 institutions, 29 institutions permitted interviews to be conducted either only with PIs or CRCs or with both.

Although permission was sought from these 29 institutions, only five of them permitted interviews with participants of clinical trials. Of the five, two were public institutions and the remaining three were private.

The selection of CTPs for the study was based on the following criteria: (a) the participant was in a trial at the time of the study, or had undergone the trial within one year prior to the study; and (b) the participant was willing and had consented to be a part of the study.

3.3. Data Collection Tools

Since Sama has been engaged for a long time in a multi-site study[35] looking at the perspectives of participants in clinical trials, a set of data collection tools/instruments had already been developed and approved by the Ethics Committee of Sama. These instruments—interview schedules—were adapted and then prepared to assist the study team in their interviews of KIs and CTPs. Interviews were conducted with participants of clinical trials using the method of layered consent (as illustrated in 3.4 Research Ethics Obligations, below). Access to participants was provided in four of the six states, details of which are provided in the Table 1.

Table : 1

	State	Number of participants with whom interviews were conducted		Total
		Women	Men	
1	Maharashtra	0	4	4
2	Andhra Pradesh	3	1	4
3	Gujarat	2	4	6
4	Rajasthan	0	3	3
	Total	**5**	**12**	**17**

Note: No clinical trial participants were interviewed in Delhi and Uttar Pradesh.

3.4. Research Ethics Obligations

The process of consent taking was implemented at multiple levels

1. The study objectives and the interview protocols were submitted to the institute/hospital, which then forwarded these to the ethics committees of the institute/hospital and obtained approvals to interview the KIs and CTPs.
2. At times, the study objectives were presented physically before the EC of the institute/hospital to obtain approvals.
3. The research team also spoke to the heads of department (HoDs) and the principals of the institutes/hospitals for approvals.
4. The research team spoke to the PIs directly for permission to interview the CTPs.
5. PIs in private clinics sometimes first speak to CTPs and inform them about the research study, following which the research team takes consent from CTPs as per research protocols.

3.5. Ethical Framework

Securing informed consent was a key component of the study. In the process of obtaining consent, the researchers provided information about the study and its aims and objectives, provided assurance of confidentiality/anonymity and described the future use of the data being collected, gave the estimated timeframe for the interview, etc., to enable respondents to decide whether they would be willing and able to participate. The consent forms were drawn up in English and in other Indian languages such as Hindi, Telugu, Urdu, Gujarati, and Marathi, based on the location of the research study site. The researchers also sought prior consent for audio documentation of the interviews, which was done only after obtaining express permission from the interviewee. The ICF was signed both by the interviewee and the researcher, and a copy of the signed form was given to the participant. This process was carried out prior to each interview.

Participation in the study was completely voluntary and the prospective participants were duly informed about their right to withdraw at any point during the interview or to not respond to certain questions if they so desired. The confidentiality of KIs and participants was maintained throughout the research study. Anonymity was ensured by the use of codes in the process of data entry, data presentation, data analysis, etc.

3.6. Data Analysis

Interviews were analysed to identify emerging themes and codes were independently developed and then discussed in order to spot and track convergence. For the purpose of analysis, the fully documented interviews were categorised and entered into Microsoft Excel spreadsheets. The study findings were divided into chapters that reflected or examined the emerging themes of the study. A framework for chapter organisation was developed after much discussion, and each chapter was assigned to the researcher most equipped or inclined to analyse that particular theme, for instance, informed consent.

3.7. The Challenges Encountered during Research and Fieldwork

- Several institutions that were clinical trial sites refused us permission to meet with CTPs, PIs and other relevant KIs.
- While some institutions permitted interviews with KIs, they were unwilling to facilitate or provide access to participants in trials being conducted by their personnel. The reasons for not permitting access were varied: 'it is against the policy of the hospital'; 'we do not have any ongoing trials'; 'we are worried about confidentiality'; 'information about participants is highly confidential'.
- Gaining access to CTPs was thus a very challenging task, given that the key pathway to gaining access to them was through the institutions in question and their KIs.

- Conducting repeat interviews with CTPs was seldom possible because of their lack of time or interest. Only in a few cases were we able to conduct in-depth repeat interviews.
- Even in situations where the team members were able to speak to the CTPs, since the process was one of layered consent, access was restricted to only those participants who had been chosen by the PI or by the CRC, thereby often introducing the risk of bias.
- Another risk is the fact that the identity of the participant is already known to the PI. The research team took the necessary safeguards to ensure that the PIs would not gain any access to the information provided by the CTPs. The anonymisation of the CTPs was an essential and crucial factor in this study.
- The team tried to conduct interviews with the participants, if and where possible, at a neutral venue of their choice, away from the presence of the hospital staff, to minimise any constraints in speaking freely.
- At some sites, access was delayed or denied, as the research team was required to present the research findings of the study to the EC of some of the institutions that were approached. While some ECs did not give permission, the process was also delayed because the meetings of the ECs in some institutions were not held within the timeframe of the present study.

4

Profiles

There are many people and processes involved in clinical trials. The sponsors are responsible for arranging and funding the trial. The CROs help the sponsors design the trial, obtain the required approval from the relevant authorities, monitor the clinical research, and coordinate activities with the insurance companies and the central laboratory organisations where the blood is sent for testing. The PIs, who are qualified medical practitioners, follow the guidelines laid down under the various regulations as well as the ICMR guidelines for the conduct of clinical trials. The CTPs voluntarily enrol themselves in the clinical trial. The regulators play an important role in implementing the laws and regulations that govern the conduct of clinical trials. The profiles of the various players in the clinical trials examined in this study are discussed below.

4.1. Pharmaceutical Companies

At present, as per CTRI, ten Swiss pharmaceutical companies are in the process of conducting clinical trials in India.

A total of 199 trials were registered by these ten companies, ranging from one trial to 114 trials per company.

Brief profiles of the trials by the top four Swiss pharmaceutical companies—Novartis, Roche, Actelion, and Sandoz—are given in Table 3.

While several of these trials are being conducted only in India across multiple sites, others are global multicentre

Table : 2

	Name of pharmaceutical company	Number of sponsored clinical trials in India
1	Novartis	114
2	Roche	56
3	Actelion	7
4	Sandoz	9
5	Serono	5
6	Octapharma	2
7	Galderma	2
8	Ferring Pharmaceuticals	2
9	Cilag AG	1
10	Janssen Cilag	1
	Total	**199**

trials being carried out in a number of countries, including in the Indian subcontinent. However, very few of the trials relate to neglected diseases.

Table : 3

Company	Trials
Novartis	Trials at different phases, mostly at Phase III, post-marketing, and Bioavailability (BA) and Bioequivalence (BE) studies,[36] and a few at Phases I, II, and IV. None of the trials relate to neglected diseases. One trial relates to Type II diabetes. Apart from this, the company's trials are for drugs for the treatment of cancer, schizophrenia, psoriasis, pulmonary, renal, and other illnesses and diseases.
Roche	Most trials at Phases I and III; a few at Phases II, IV/post-marketing; and BA/BE studies. None of the trials relate to neglected diseases. The main focus of research is on therapies for cancer, rheumatoid arthritis, schizophrenia, and measles/mumps.
Actelion	Trials at Phase III; randomised, parallel group, placebo-controlled trial for ulcers; trial for hypertension in children.
Sandoz	Trials at Phase III for breast cancer.

Approximately 13 CROs were involved in the trials conducted by the ten Swiss pharmaceutical companies in India, which range from large players claiming operations in more than 40 countries to some that have a presence only in India. They are:

- Quintiles
- Lambda
- Veeda Clinical Research Private Limited
- Lotus Labs Private Limited
- Manipal Acunova Clinical Research Centre
- Max Neeman International
- Inventiv International Pharma Service Private Limited
- Jubilant Clinsys
- INC Research
- Clintec (India) International Private Limited
- Pharmasourcing i3
- Pharmaleaf India Private Limited
- CIDP Biotech India Private Limited

Organisations such as Pharmasourcing i3 and Pharmaleaf India Private Limited provide specialised services or have their own USP, for example, in sourcing human resources for clinical trials and in "advising on regulatory strategy". CROs, for their part, also work in collaboration with other players to provide specialised services. For example, Jubilant Clinsys is working with ClinPhone, a clinical technology organisation (CTO) that develops and manages Web-based clinical trial management information systems.

4.2. Study Participants

A total of 17 CTPs were interviewed. Twelve were men and five were women, all in the 25-75 year-old age group. The participants were from the Hindu, Muslim, Christian, Jain, and Parsi communities.

Seven participants had studied up to secondary school level, that is, class 9 to class 11. Six were graduates, including one participant who had completed an engineering degree and another who had a postgraduate diploma in education. Eleven participants were married and lived with their families. Of the remaining six participants, two (one man, one woman) had never married, while four participants were separated or their spouses had died. The participants were involved in a range of work/occupations—home-based stitching/sewing, farming, teaching, running small businesses (grocery shop, car rental), working in a bank, etc. Two participants were retired, three of the women participants were housewives/ homemakers, and one participant was a student.

About half of the participants lived with their families, which were not limited to their spouses and children, and were invariably the sole or substantial contributors to the household income. Five participants (including the three housewives) were financially dependent on their husbands, children, or other family members.

The socio-economic profiles of the participants differed in each study site owing to the nature of the hospital approached. For example, in one location, the hospital that gave us permission to interview CTPs was a large private hospital. Here, the CTPs were from both the middle and upper-middle classes. In cities where the research team interviewed CTPs in a government hospital, the participants invariably were from the lower and working classes.

Table on profiles attached as Annex II.

5

Recruitment of Participants for Clinical Trials and Conflict of Interest

An important part of a clinical trial is the procedure by which humans are recruited to participate in it. It is essential that the CTPs volunteer to participate in the trial, and are not influenced by monetary considerations nor act because of the undue influence of the doctor/physician who may persuade them to enter the trial. In cases where the doctor/physician succeeds in persuading the individual to enter the clinical trial, care should be taken to ensure that no undue influence has been exerted on the CTP and that the doctor/physician does not face any conflict-of-interest issue. The highest ethical standards ought to be followed while recruiting humans for clinical trials.

5.1. Sourcing and Recruitment

Sama's findings with regard to the sourcing and recruitment of humans in clinical trials are as follows:

According to the KIs, all the CTPs[37] were recruited through multiple sources such as outdoor patient departments (OPDs), indoor patient departments (IPDs), and health camps.

> *"All our patients are sourced through our OPDs and sometimes from IPDs."*
>
> *"We recruit patients from our OPD through the randomisation process. We select them on the basis of the inclusion criteria of the protocols."*
>
> *"All my trial subjects are from my own clinic OPD. I have extensive experience from 40 years of practising medicine, so, naturally, I have a large network of patients. So I never have a problem in recruiting participants. In addition, since my hospital has other skilled doctors from various branches, we run trials for those diseases also."*

> *"It is easy for us to recruit subjects since we are doing trials in the government hospital where we have a large pool of patients and I personally have a mammoth OPD every day from which I can select participants. Recruitment for any clinical trial is never a worry for me."*

The doctors, apart from recruiting patients at their own clinics, also inform other doctors about the trials and recruit their patients if they meet the inclusion criteria.

> *"Research subjects are sourced through the OPD and referenced from the other doctors. We speak with other doctors in the hospitals and ask them to refer any other participants to us that appear to fulfil the criteria. We share a snapshot of the trial with them so that they can help us in the recruitment for the trials."*

One clinic said that it sourced participants through an advertisement, while another denied taking this approach.

> *"We also at times may put an advertisement in the paper, but only after receiving the approval of the sponsors and of the EC."*

> *"Most of the time, the patients for all clinical trials conducted at the hospital are sourced from the principal investigators' OPD itself. There is no need for us to advertise or hire agents for this purpose. We have a vast resource at our disposal. Why should we advertise?"*

Two clinics claimed that they source patients from or through health camps, which are organised by the hospitals in nearby villages and towns.

> *"We generally organise health camps in rural areas and in nearby towns for health check-ups, including heart-related check-ups. During the check-ups, we identify patients and ask them whether they would like to be a part of the trial."*

> *"We organise health camps and now we want to extend these camps to mental health as well. We can also recruit patients for our trials from these camps in future."*

According to the KIs, sometimes the CTPs also source participants for trials.

> *"Many of my trial subjects bring in their relatives and friends for enrolment in the trial because of the access to free treatment."*

Participants also come to know about the trials from OPDs, IPDs, relatives and friends, and through health camps.

> *"XXX hospital had held a health camp in my community in Gujarat where I was diagnosed with three blockages and was asked to undergo bypass surgery. Since I have very limited resources, I could not undergo bypass surgery. Then after three months, some lady asked me to come down to another city in Gujarat for free treatment through a trial."*

> *"I had been suffering from this skin problem for years. No medication worked. My friend advised me to go to this particular hospital, which has a good dermatology*

> *department. I visited the OPD for a few months. One day, the PI told me in the OPD that there is this trial for a new drug, and asked whether I would be interested in participating in it. I said yes."*

The majority of the participants interviewed entered the trial because of their physician. When the trial's PI is also the person's primary physician, there is a conflict of interest, especially if physicians are paid recruitment fees for recruiting their patients into trials. According to the SOMO[38] report, in many trials:

> *"the dual role of care giver and principal investigator is also questionable as principal investigators often receive monetary benefits to conduct the trial. The benefit may be a fixed amount of money for each patient that the investigator recruits for the study or per patient that completes the study, or may be provided 'in kind' by means of (expensive) gifts [given] to the investigator or [to] his/her institution (interview with clinical investigator)."*

Sourcing patients from OPDs and IPDs is the traditional way of conducting clinical trials, and is a worldwide practice. However, when the doctor/physician acts as the PI for a clinical trial, he/she may have enough authority to dominate the patient and influence his/her decision to enter or participate in the trial.

While no country has prohibited physicians from being investigators and from recruiting their own patients as participants in clinical trials, some countries have instituted regulations (a) to separate the clinical space from the research space in the hospital; and (b) to not allow physicians to obtain informed consent. Indeed, there is a gross conflict of interest (CoI) in care-cum-trials, particularly in communities where poor and uneducated patients are enrolled as participants of clinical trials. It is difficult to imagine that a patient under care would refuse to participate in a trial being conducted by the attending doctor. Further, the practice of doctors/treating physicians recruiting their patients for participation in a clinical trial is a clear conflict of interest. Conflict of interest is defined as "a discrepancy between the personal interests and professional responsibilities of a person in a position of trust".

5.2. Conflict of Interest

In the USA, in the case of Moore v. Regents of the University of California, 793 P.2d, 479 (Cal. 1990), the plaintiff's cells were used in potentially lucrative research without his permission. The plaintiff alleged that the physician had failed to disclose his pre-existing research and economic interests in the cells before obtaining consent to the medical procedure by which these cells were extracted. The disclosure obligation of the physician was the core issue decided in the case. The California court held that it is the obligation of the physician to disclose his/her personal interests to his/her patient as this may affect the physician's professional judgement. The court concluded that: (1) personal interests unrelated to the patient's health, whether research oriented or economic, may affect the physician's professional judgement; and (2) the physician's failure to disclose such interests may give rise to a cause of action for performing medical procedures without obtaining informed consent or for breach of fiduciary duty. In Canada, in the case of R. v. Zlatic,

[1993] 19 C.R. (4th) 230 (Can), the principles of what amounted to fraud were laid down, and it was held that any means that could be characterised as dishonest by the objective standard of a reasonable person would suffice to reach this conclusion.

Thus, it is essential that doctors and physicians who are also PIs, or who participate in clinical research, disclose their financial interests and the recruitment fees that they receive from the sponsor to the approving/ licensing/ regulatory authorities, the EC, the IRB, and other concerned bodies, before the commencement of the trial. This step is important so that all conflict-of-interest issues can be addressed, so that patients are not recruited due to the undue influence of doctors and physicians, and so that their vulnerability is not taken advantage of by the entire research team, including the sponsors and the pharmaceutical industry as a whole.

5.3. Ethics Committee

The EC plays an important role in the conduct of clinical trials. It is now widely accepted that research involving human participants should be conducted only after an appropriate ethics review has taken place. Hence, the EC and the IRB need to play a significant and proactive role in assessing the potential conflict of interest among all the parties involved in conducting clinical research, and to prevent such practices from occurring. The EC and the IRB need to review the financial considerations or incentives provided to the doctor/ physician by the sponsor to recruit patients into the clinical trial.

Some of the IECs function well at a few sites, but even their work is not completely transparent. The IECs make very little information on their work and performance available in the public domain, thereby reducing public confidence in their work.

Registration of Ethics Committees by DCGI[39]

The revised Schedule Y of the Drugs and Cosmetic Act [Section 2.(5) Schedule Y] devotes significant attention to the roles and responsibilities of ECs, prescribes the composition of ECs as per the ICMR guidelines, and provides formats for the approval letter of ECs (Appendix VIII). According to a notification released by the Ministry of Health and Family Welfare (Department of Health) on 8 February 2013 [G.S.R 72(E)], in the case of the registration of ECs, no EC shall review and accord its approval for a clinical trial protocol without prior registration with the Licensing Authority as defined in Clause (b) of Rule 21 under 122DD of the Drugs and Cosmetics Act. Furthermore, the EC shall review and accord its approval for a clinical trial and also conduct an ongoing review of the trial at appropriate intervals as specified in Schedule Y and in the Good Clinical Practice Guidelines for Clinical Trials in India and in accordance with other applicable regulatory requirements for safeguarding the rights, safety, and well-being of the trial subjects.

Also, the requirements and guidelines for registration of the EC, mentioned in the same notification, include the requirement that the EC shall review every clinical trial proposal, evaluate the possible risks to the subjects, and assess the expected benefit and the adequacy of the documentation for ensuring privacy, confidentiality, and justice. In the case of any SAE occurring to the clinical trial subjects during the clinical trial, the EC shall analyse the situation and forward its opinion as per the procedures specified in Appendix XII of Schedule Y of the DCA.

In addition, some IECs have an irregular schedule of meetings, do not follow any SoP, and their membership does not meet GCP guidelines. It is important that the IECs and the IRB also be made legally and morally responsible. Similarly, it is important that all the relevant details of the CTPs appear on the ICF that they have signed, that the CTPs understand what they have agreed to undertake and what the PI, the sponsor, the funder, etc. are responsible for, so that they are equipped with the necessary knowledge and power to make legal claims on the latter for any breach of their duty to care for, and for any dereliction of their duty to ensure the safety of, the clinical trial participants.

Therefore, there is a greater need for the EC and the IRB to carefully scrutinise the ethical issues, the financial issues, and the conflict-of-interest issues facing or involving PIs and institutions before the commencement of a clinical trial. The budgets of clinical trials need to be scrutinised carefully before the research trial is allowed to begin. A central monitoring system needs to be developed and implemented to prevent malpractices. Courts in the USA and in Canada have held that the actions of doctors or physicians who are investigators and who have a personal interest in the outcome of clinical trials and who do not disclose their interests in such trials amount to actionable wrongs of fraud and dishonesty. Often the patient's right to autonomy is overlooked, the need to adopt safety measures to ensure the patient's health and well-being is ignored, and high risks are taken. This situation arises even though the Belmont Report[40] states that the least risky procedure and option should be undertaken. This also violates the constitutional right to life guaranteed under Article 21 of the Constitution of India.

6

Reasons for Entering or Participating in a Clinical Trial

Before joining the trial, the participants must qualify for the study. Some research studies require the CTPs to have a certain illness or to exhibit certain conditions that need to be researched in the trial, and also require some healthy participants. "Inclusion criteria" and "exclusion criteria" determine which participants will enter the trial and which will be excluded from it. These criteria are also supposed to ensure the safety of the participants and ensure that the research study is conducted as planned.

6.1. Motivations for Entering or Participating in a Trial

Sama's findings with regard to the motivations of multiple stakeholders in participating in/conducting clinical trials revealed that there are many reasons for the participants' willingness to participate in a trial.

> *"Most educated urban patients refuse to participate in the trials and constitute only 20 per cent of the trial participants. The larger portion of trial participants is mainly rural and constitutes 80 per cent of the total."*

The entry into a clinical trial ushers the participant into a process characterised by challenges and difficulties, as well as optimism and hope.

> *"Since this hospital caters largely to poor patients, a large majority of my patients who come to the rheumatology OPD cannot afford the new-age 'biologics' treatment for arthritis. These new treatments go beyond the use of disease-modifying agents and are generally more expensive medications given in injectable form when patients stop responding to oral medications. This treatment is extremely expensive and is unaffordable for almost all my patients. Thus, when we get a proposal for conducting a trial using this form of treatment, we consider it for the benefit of our patients. These patients can be brought under the trials."*

Many KIs said that it is not very difficult for them to recruit participants as the trials provide free or affordable treatment and medicines, and promise a possible cure to participants who otherwise cannot have access to treatment.

> *"The biggest incentives are free medicines and free investigations. People participate in drug trials because they feel that this particular drug being tried may help in finding a better cure and also [will] take care of their investigations for free. The promise and the possibility of a better drug drive them to participate."*

> *"We have seen it ourselves that trial subjects often do better as compared to patients following the regular treatment. We found that the survival rate was much higher."*

6.2. Participants' Perspectives

> *"I could not afford the treatment for my illness. When I was told that there was this trial which is free of cost, I decided to enrol."*

> *"I underwent bypass surgery in this hospital. After the surgery, I was regularly coming here for my check-ups. During one such visit, the doctor told me about this trial and told me about this drug that could be beneficial for me. If I agreed to participate in the trial, all my check-ups and the drug would be free. The doctor also told me that if the drug does not do any good, it would not harm me either. So there was nothing to fear. I thought if it is beneficial to me, why wouldn't I take that drug? There is nothing more important than my health."*

Some of the participants' perspectives also reveal that they perceive their participation as treatment rather than their undergoing a trial. Besides the desire for receiving treatment, the other motivating factors include the participant's trust in the doctor, the reputation of the doctor, the quality of health care services available, and the attention the patient receives from the doctor.

> *"I'm really happy to be in the trial as Doctor Saab spends a lot of time on my check-up and gives me free medicines."*

> *"Doctor Saab told me that this will work for me and treat my disease, and I said yes."*

> *"After my doctor told me about this new treatment, I decided to take part in the clinical trial."*

The above quotations clearly illustrate the misleading information that the CTP receives from the doctor. When the drug is an investigational drug, how can the PI claim that this will treat the patient?

Similarly, PIs also have some personal interest in conducting clinical trials.

> *"All pharmaceutical companies give us some money to conduct trials in the institution. However, it is meagre. At my site, I keep many coordinators so that clinical trials are conducted properly at the site, documents are complete, data are maintained well—and this requires money. So in my case, we could say it is tough to make both ends meet. We spend as much as we receive. It can't be a profit-making mechanism. As a PI, I do not get much incentive monetarily, but I definitely learn a lot when I undertake a clinical study both from the patient's perspective as well as from the point of view of medicine. Further, these studies when published outside bring a good name to the institute, to my team, to my doctors, to everybody. At times, the drugs work a miracle for the patients, and it gives us much happiness to be able to provide advanced new treatment to our patients long before it reaches others. So it would be wrong to say that clinical trials are conducted only for money. It is necessary to do research as that is the only thing that takes everyone forward."*

> *"We rarely get these opportunities to be a part of global clinical trials. When I got this opportunity, I was very happy. And I am sure once we get the results we will publish it in international journals."*

PIs from public hospitals and institutions said that they do not gain any personal monetary benefit from participating in a trial. The money goes directly to the hospital or to the institution's fund. A PI from a public institute said:

> *"We believe in drug development and ethical conduct. Trials are not meant for our personal benefit, nor do we get money from the sponsor. Many private physicians will get money per trial/per patient individually, and often they end up conducting the trial unethically."*

A PI said that many clinical trial participants participate in trials to get good medical check-ups, as they receive better treatment in the context of a clinical trial than they do in a public hospital. This view was also expressed by a participant:

> *"In a public hospital, generally the OPDs are crowded, and the quality [of care] is also very poor. Most often the drugs are prescribed and the diagnostic tests are done from outside, and we have to pay from our own pocket for both drugs and diagnostics. Whereas in clinical trials, we don't need to pay for tests or drugs. There is no crowd, and we get enough attention and follow-up."*

The participants entered into clinical trials mainly to escape the burden of poverty and the non-affordability of the treatment. In cases where no cure was available or where treatment options were expensive, hope and optimism were motivations. The provision or availability of free medicine, free treatment, and quality services for clinical trial participants rather than for patients was also a motivating factor. The exploratory study, even within its limited ambit, raises important questions regarding the category of people accessing these facilities. The provision of medicines as part of 'free treatment' cannot be viewed and comprehended in isolation, as there are other larger social and economic factors impacting the everyday lives of these individuals.

7

Informed Consent

Informed consent is the process of informing the participants in a clinical trial of the risks and benefits of the trial, the possible side-effects, the adverse effects, the alternatives, the duration of the trial, the number and interval of the doses of the drug required to be taken, the number of tests required to be done, the impact of the drug on pre-existing diseases or ailments, the freedom to withdraw from the trial at any time, etc. The patient needs to understand all this in a language that he/she understands and in the same sense as the doctor understands it, and only then should he/she give consent. Consent given blindly, without understanding, or because the patient has full faith in the doctor, is not consent in the true legal sense.

The Supreme Court (SC) of India has also explained the meaning of informed consent for treatment. In Samira Kohli v. Prabha Manchanda, AIR 2008 SC 1385, the SC held that doctors are authorised to perform only those procedures for which express consent has been given, the only exception being the doctrine of necessity. The SC further held that doctors have to furnish adequate information to the patient to enable the patient to make a balanced and well-informed judgement as to whether he/she should submit himself/herself to that particular treatment or not. The doctor should disclose: (a) the nature and procedure of the treatment and explain its purpose, benefits, and effects; (b) the availability of alternatives, if any; (c) the adverse consequences of refusing treatment; and (d) an outline of the substantial risks.

The SC held that the patient has an inviolable right in regard to his/her body and has the right to decide whether he/she should undergo a particular treatment or surgery or not. The patient should have the capacity to consent, consent should be voluntary, and consent should be given on the basis of adequate information concerning the nature of the treatment procedure so that he/she knows what he/she is consenting to. Consent given for a diagnostic procedure cannot be considered as consent given for a therapeutic procedure. Consent given for a specific treatment procedure will not be valid for conducting some other treatment procedure.

The most important purpose of the ICF is to ensure that CTPs have ample knowledge of the benefits, risks, or side-effects of the drug in order to make a decision about whether

to begin or to continue participation in a clinical trial. The informed consent process does not end with the signing of the ICF. During the trial, CTPs must be encouraged to ask questions at any time.

Sama's findings based on the interviews with KIs and CTPs reveal many interesting experiences and perspectives relating to the process of obtaining informed consent.

KIs expressed their frustration with, and their concern about, the way in which the ICF has been developed and used.

> *"The consent form goes into 20–30 pages. It is too detailed and very difficult to explain to the subject. When as a PI I explain to the subject the contents of this 20–30-page-long ICF, often I feel that I am confusing the patient with all this information. However, I do my bit. Then the patient is given the form, to take home and study the contents, and asked to return after a week. I wonder how much he or she can understand the technicalities. We give them the form in the local language and tell them to look at it and read it carefully. Sometimes we had this experience where four out of ten patients refuse after reading the ICF."*

> *"As an investigator, I prefer the ICF to be very concise and not more than three pages, with some relevant information. It should be in a simple language which can be understood by the subject. Since the ICF comes from the sponsor, and is approved by the EC, I have to follow it as it is. Moreover, if it is a global trial, some questions are irrelevant and not contextualised. The IC forms should be developed as country-specific forms and should be approved by the Ethics Committee."*

> *"A consent form should not be more than two pages and should be tested using a 'readability system' as is done in the US or the UK. This document should be the primary document on which the consent should be taken. A detailed document about the study should be available to the patient if he or she would like to read through the fine print."*

> *"Sometimes it is very difficult to convince the patients to agree to the study and to sign the document. In our country, signing a document makes anyone nervous. There is an amount of mistrust and they keep wondering why the doctor is giving so much information, there must be something wrong with the drug."*

The concern expressed here is about whether the technical information is understood by the patient; whether the CRC and the PI are able to spend enough time explaining all the details to each patient; and whether the patient is able to understand all the details and is able to clarify doubts or express concerns, if he/she is at all in a position to do so.

> *"Patients are not educated. So it takes time. We need to give them a lot of time. Follow-up is very important as patients should not drop out of studies, as this leads to a bad research study. Research data should not be manipulated—the quality of research findings from India is often questionable. These issues can be avoided if the patient is educated and well informed about his role as a participant, and understands the trial, compliance, how to take the drugs, how to come for follow-ups, etc. India has more patients than any other country in the world."*

Another KI said that the IC-taking process has improved a lot. According to her, the PIs have also now understood the importance of informing the CTPs about all the components of the study—the drug, the known side-effects, why they are being asked to participate in the trial, the number of visits required—during the IC-taking procedure.

> *"Earlier, patients would participate in trials just because the doctor had asked them to. Though patients still have full faith in their doctors, I am seeing a difference in attitude. Patients and/or their attendants are asking more questions regarding the study before making any commitment. The PI also has to provide a comfort zone for the patient to exercise his right to query, and these systems are more in place nowadays. Patients' education levels are also improving, and so they are more proactive in asking questions regarding trials."*

7.1. Participants' Perspectives

A close examination reveals several gaps between the official rhetoric and the reality on the ground. Interviews with participants provide a contrasting picture.

> *"The centre had given me several forms which were all in English. I didn't read them thoroughly. I just signed and gave them back as I completely trust Dr. XXXX. Also, the assistant doctors informed me that I would be given one more copy, which I could keep with me and show my parents. But I have not yet collected my copy. I think the form has general information about health and has some basic answers to questions pertaining to my health. Dr. XXXX devoted so much time in explaining everything about the treatment."*

> *"The form was partly in English and partly in Marathi. I come from a small village and had no one who accompanied me. I didn't have anyone to whom I could ask questions or to whom I could turn to get my doubts clarified, so I had no choice but to sign the form. I did not understand many points in the form. And I don't remember anything about the form."*

> *"They called me to Ahmedabad and I understand that they are doing a 'course' of the medicine on me, but I don't know anything else. They gave me a form of five–six pages in Gujarati, which I read and signed. There was no one with me and it would have been difficult to take back the form and then return again."*

> *"Yes, my son did sign the papers. Dr XXX explained to us in Hindi that we had agreed to take part in the trial. I am participating in this trial of my own free will. A copy of the informed consent form was given to my son who read it and signed it on my behalf. I don't know if there is an option to withdraw from the trial process or if there is any mention of insurance. They also told me that I will have to report on whichever date they ask me to."*

In several of the interviews conducted, respondents pointed out that an ICF has limited value in the Indian context, as most of the patients are illiterate and cannot understand the contents of the form. Problems with comprehending the ICF on the part of the proposed

CTPs and inadequate translations of the ICF were also highlighted in interviews with several participants. Whether the informed consent process has been implemented in line with the relevant ethical guidelines has not been verified by the authorities. Because of privacy considerations affecting the CTPs, the monitoring of the informed consent process, by the EC or by other authorities, stops with the PI. The PI collects the ICF, while the authorities, and in some cases the EC, check whether they are signed. However, the level of understanding or awareness on the part of the CTPs about the trial or the associated risks is not independently verified.

8

Adverse Events

Adverse events (AEs) and serious adverse events (SAEs) are untoward medical occurrences in a patient or CTP who has been administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. AEs are a matter of great concern in ensuring the protection and safety of human subjects who are participating in a clinical trial for the testing of an experimental drug or device. Some of these AEs are life-threatening and may also result in the death of the clinical trial participant. Some AEs are suspected of having occurred, or there is a reasonable possibility of their occurrence, whereas other AEs are unexpected, and hence the possibility of their occurrence is not specifically mentioned in regard to the drug under investigation. Investigators or PIs are obliged to report such AEs or SAEs during a clinical research study or trial.

Many clinical trial studies in India in the past had led to concerns over the reporting of AEs or SAEs. There is a lot of ambiguity in the reporting of AEs or SAEs even today.

8.1. Procedure for Reporting Adverse Events or Serious Adverse Events

Sama's findings based on interviews with CTPs with regard to AEs and SAEs are as follows:

> *"I had pain in the chest for some time. Then my son made a call to the hospital. They told me to come to the hospital immediately and get admitted. I was admitted for three days and I was discharged today."*

> *"I was told by the doctor not to take any medicine from other doctors. I was asked to inform him immediately if this happened. The CRC gave me his number and asked me to call him if there was any health problem during the trial period. Once I had fever and I called him and he advised me to take Paracetamol only. I was okay after that."*

> *"When I had fever, headache or giddiness I inform the CRC or the doctor, they give me the medicines. Sometimes I call them over phone and get their advice."*

In some cases, in addition to being told to attend the regular follow-up sessions, participants were also instructed to report to the trial site in the situation of any AE, including cold, cough, fever, or any other event.

Interestingly, according to a few KIs:

> *"Side-effects are a way of life nowadays. Everything that we use in our daily life has an effect on our body. Whatever we eat is adulterated. The water we drink, the air we breathe is polluted. Each medicine has a side-effect. However, the side-effects should not be out of proportion to the beneficial effects. We assure the patients that these symptoms shall disappear."*

> *"Patients following the regular treatment procedure may live for another three months, while those on the trial may survive for another six months. SAE in both these cases is inevitable. Hence, if we compare these two scenarios, we find that clinical-trial patients have had their life span enhanced as compared to those who were not trial participants."*

From the interviews cited above, it is evident that the doctors appear to be casual about SAE reporting. In a way, they underestimate the importance of the responsibility placed on their shoulders by comparing the task of SAE reporting with the problem of dealing with polluted air/water. They forget that they are dealing with a chemical or drug or other medical tool/intervention that is under investigation, and that they have a duty towards their patients. In addition, they also forget the fact that based on the data they collect, analyse, and submit to the regulatory/licensing authorities, these drugs will be approved and used widely for treatment.

8.2. System of Reporting of AEs and SAEs

The KIs stated that, in the case of any SAE, they are bound to report to the EC within 24 hours and also inform the sponsor. However, some of them also stated that this is possible in the case of institutions, which have in-house ECs, but is not always possible in the case of private practitioners who are conducting trials independently and who have received approval from independent ECs from outside their clinic/hospital.

> *"In the case of AE, we have to notify the sponsor depending upon the severity of the adverse effect, for example, if the headache persists over a longer period of time. We have to, in both cases, report the AE/SAE to the sponsor and the Ethics Committee within 24 hours. The assessment of the AE is done by the PI, and if it is found that the AE is related to the trial drug, then sometimes in the case of a global study, even the global team at times would be present to assist the PI and the co-PI."*

A KI from a small clinic said:

"Yes, it takes time. The EC meets once in six months and addressing any issue related to a trial will get delayed. However, I try to inform my CRO representative."

Another KI from a small centre also reiterated that his job is to report to the CRO. All the data are given to the CRO. The CRO will only process and analyse the date and send them to the sponsor.

An important aspect of clinical trials is the reporting of SAEs and deaths that may occur during the trial and perhaps also due to the trial. A uniform system of reporting is essential to monitor the practices and facilities being made available to clinical trial participants. At present, various pharmaceutical companies and CROs are using multiple/different formats and procedures for reporting SAEs to CDSCO. Although most reports adhere to Appendix XI of Schedule Y, the use of multiple formats as well as missing information – including improper referencing for the submission of follow-up reports – have led to difficulties in segregation and in the further processing of these reports by the CDSCO office.[41]

Table : 4

	Categories	No. of SAEs 2010	No. of SAEs 2011	No. of SAEs 2012
1	Anti-cancer	226	139	66
2	Cardiovascular	368	229	82
3	Cerebrovascular	28	11	5
4	Anti-diabetic	11	31	12
5	Antiviral/Antifungal	5	12	8
6	Others	30	16	38
	Total	668	438	211

Source: Response from DCGI to Lok Sabha and Rajya Sabha's questions

According to the data made available by CDSCO, the number of patients enrolled in clinical trials that died in 2010, 2011, and up to June 2012 were 668, 438, and 211 respectively. However, the number of SAEs resulting in death due to clinical trials reported in 2010 and 2011 were 22 and 16 respectively. The number of death related to clinical trials in 2010 was initially reported as 25, in which nine companies were involved. Subsequently, it was revealed that in two cases, the deaths had been reported twice for the same patient. Further, in one case, the EC and the investigator later clarified that the death was not related to the clinical trial. Thus, there were 22 death attributable to clinical trials in 2010 for which compensation was paid by the sponsors/CROs. An analysis of SAEs during clinical trials in 2010, 2011, and 2012 has shown that they occurred in the categories given in Table 4.

On 20 April 2011, the Deputy Drug Controller sent notices to many pharmaceutical companies and CROs asking them to furnish information related to SAE reports. One such notice was sent to Novartis Healthcare Pvt. Ltd. [F No. CT/SAE/2011-DCG(I)] regarding reports of SAEs resulting in death in clinical trials and asked the company to urgently furnish the details of the seven reported cases:

1. *the subjects who had died, including their names and backgrounds*
2. *the details of the site, including the name of the investigator and details of the compensation paid; in case no compensation had been paid, the reason for this*
3. *the opinion of the Ethics Committees on the SAE reported for the seven cases that had occurred in 2010.*

CDSCO has issued a notification with the aim of achieving uniformity and completeness of data with respect to SAE reporting in clinical trials.[42] According to the notification released by MoHFW (Department of Health) on 1 February 2013, any report of SAEs occurring to the subject during clinical trials, after due analysis, shall be forwarded within 10 days of its occurrence, as per Appendix XI and in compliance with the procedures prescribed in Schedule Y of DCA.

Further, in the case of injury or death suffered by the subject during the clinical trial, the applicant shall provide complete medical management and compensation in the case of trial-related injury or death in accordance with Rule 122 DAB and the procedures prescribed under Schedule Y. The details of the compensation provided in such cases shall be intimated to the Licensing Authority within 30 days of the receipt of the order of said authority.[43]

9

Compensation and Insurance for Participants of Clinical Trials

The compensation for AE, SAE, and death of the clinical trial participant should be determined prior to the commencement of the trial. All parties – sponsor, researcher, funder, EC, and IRB – are accountable and responsible for ensuring that the CTPs are compensated on time and adequately without unnecessary delays and hitches.

9.1. Who Decides the Amount of Compensation to be Paid and When?

Most of the participants had no knowledge of the element of compensation or insurance involved in the trial.

> *"The PI informed me that it was a trial and that compensation will be paid if any casualty occurs during the course of the trial. All lab procedures and visits related to the injection would be free of cost, including the injection itself. And that I would be reimbursed for all my travels to the hospital."*

> *"I had read through the document thoroughly. There was some mention about compensation with regard to death and the reimbursement of all treatment costs if the need arises."*

> *"What death? What treatment? I did not get any side-effect and I am doing very well with these drugs. . . they said they would give me treatment for free if something went wrong. Something was written about it in the document too. I don't remember much. Dr. XXX takes full care of his patients and I am happy with him."*

However, a CTP expressed his disappointment:

> *"Initially I was told that the travel fare from my village to Pune and back would be paid to me but till now they have not paid me anything. When I came here for the first time the assistant doctor was different, he had promised to pay me for my travel, but now there is a lady doctor and it is difficult to talk to a lady about all this. I feel awkward to ask the lady doctor about the ticket fare".*

Sama's findings are based on the responses of PIs, which varied from case to case, and thus the entire issue of compensation in the case of injury is ambiguous.

> *"The PI usually decides the amount of compensation to be paid to the patient or to his family. The calculation of compensation is usually decided on the basis of three main factors—the age of the person, his earning capacity, and the number of dependents of the patient."*

> *"The PI primarily decides the quantum of compensation and at times may seek the approval of the Ethics Committee. The quantum is decided according to the draft guidelines of the ICMR."*

> *"Previously it was the PI who decided the quantum of compensation to be paid to the trial participant. However, now the EC members are discussing the best practices for doing this. If there is a death, the EC will decide. In the case of hospitalisation, the reimbursement will be as per actual expenditures. There have been decisions taken by the EC, but their SoP does not reflect any particular guidelines that they have followed. To the best of my knowledge, I know that the age of the deceased, the type of disease that the patient is suffering from, the stage of the disease, like terminally ill patients where death is inevitable, the number of dependents the deceased has, and the pay scale of the deceased are taken into consideration for calculating the compensation."*

The KIs attributed the responsibility of providing insurance and compensation to the sponsor.

> *"In the case of SAEs related to the trial, the compensation and the insurance are provided to the patients by the sponsor. Our EC insists on insurance when the study comes to them for consideration. We also provide insurance in the case of our investigator-initiated trials. For sponsored trials, the sponsor bears the expenses of compensation and insurance."*

> *"The EC is very strict about the insurance and compensation criteria. All protocols are very closely studied for this purpose. The insurance provided by the sponsor may include hospitalisation, further investigative tests, treatment and management of adverse events, compensation for deaths and serious adverse events, and so on."*

> *"We do not decide upon the compensation part. We just tell the sponsors that these are the guidelines of our regulatory authorities, so they have to go according to that. And if they are comfortable, then we go for the submission on their behalf, or sometimes the sponsors on their own go to the DCGI and do the submission. Whatever queries come from the DCGI, we are ready to resolve them or the sponsors themselves resolve them. So we are just facilitating the sponsor's activities. We are somewhere in between the sponsors and the sites and the regulatory authority. So it depends on what kinds of activities/scope of work is given to us by the sponsors. We are just the facilitators."*

> *"Since we provide insurance to patients, there is no question of awarding compensation for injury. We have not come across any trial-related death or serious injury so far. However, these are the responsibilities of CROs and pharmaceutical companies."*

> *"In my clinic, we have paid compensation to two patients. For these two cases, we took into account the underlying disease from which the patient was suffering, the patient's age, the patient's socio-economic status, the patient's annual income, etc. However, I feel it is a grey area and I hope that sometime soon the regulatory bodies will have some answers."*

> *"Compensation for study-related injuries is, however, not limited just to the insurance, but also extends to all hospital costs for the patient. As it is a municipal hospital, patient costs are minimal. There are no charges for beds and food, while investigative tests are subsidised to something like INR 30 (less than one US dollar) for an X-ray while most drugs are also available free of charge."*

A KI made a concrete suggestion:

> *"An independent committee may be formed of five members, consisting of one representative from the sponsor, one from the PI, one from the Ethics Committee, and two independent experts who could be clinical pharmacologists and who have worked on 'causality factors'."*

It appears from the interviews that even those who had mentioned reading the informed consent form and were satisfied with the information provided therein were unable to articulate their thoughts on compensation. This also shows the inadequacy of the informed consent forms and the incomplete or inadequate information provided by the recruiters to the patients. Furthermore, from the interviews it can be seen that all the key players in the trial had shirked their responsibility and had labelled the sponsor as the only one responsible for providing compensation.

Regulations Specific to Compensation

In February 2013, the MoHFW (Gazette Notification of Government of India [(122 DAB G.S.R. 53 (E)]) announced new amendments to Schedule Y specific to compensation. Some of the amendments are as follows:

- The phrase 'medical treatment' as of now has been replaced by the term 'medical management', which broadens the responsibilities of the sponsor in the case of SAEs such as injury, mishap, hospitalisation, etc.
- In the case of an injury sustained by the CTP, the sponsor will have to pay for medical management for as long as required.
- Financial compensation in the case of injury or death could be in the form of:
  - Payment of medical management expenses
  - Financial compensation for trial-related injury
  - Financial compensation to nominees of the trial subject in the case of death
  - Financial compensation for injury of a child in-utero in the case of participation of the parent in the trial
  - Financial compensation for injury or death in the clinical trial due to the use of placebo in placebo–controlled clinical trials
- The investigator has to now report all SAEs to the sponsor, the Chairman of the Ethics Committee, and the DCGI's office within 24 hours of the occurrence of the event.
- The amendment talks about the constitution of an independent Expert Committee by the DCGI's office 'for the purpose of arriving at the cause of death and [the] quantum of compensation for death related to clinical trials'.
- The Ethics Committee will forward its report and any recommendation on compensation for death related to the clinical trial to the Expert Committee within 21 days of the occurrence of the death.
- The Expert Committee will take its decision based on all the reports submitted and give its recommendation within 30 days of receiving the report from the Ethics Committee.
- Also, in the case of death related to the clinical trial, the Expert Committee will also recommend to the DCGI the quantum of compensation to be paid.
- The investigator/sponsor has to submit his report on the death within 10 days of the date of the occurrence of the SAE to the Chairman of the Institutional Ethics Committee (IEC) as well as to the Chairman of the above-mentioned Expert Committee.
- The DCGI has to decide the quantum of compensation within three months of the occurrence of the event of death related to the clinical trial, which the sponsor has to pay within 30 days of receiving the order from the DCGI.

9.2. Compensation and Death

In the recent hearing of a Public Interest Litigation (PIL) filed by Swasthya Adhikar Manch[44] and others, the Supreme Court passed an order reproaching the CROs/pharmaceutical companies in relation to the non-payment of compensation and the lack of insurance for CTPs. Similarly, many questions were raised in Parliament regarding the compensation to be awarded for trial-related deaths, and cases under RTI were also filed to obtain information about the compensation paid by the sponsors for trial-related deaths.

In May 2011, a committee (Government Assurances Branch (No. SQ 71/22/10/2008 – CGA)) chaired by Ms Maneka Gandhi, Member of Parliament (MP), examined the matter of compensation and found that compensation was paid only to trial victims who were injured or who had died in 2010–11. The committee found that around 438 patients had died as a result of their participation in clinical trials in 2010. However, compensation was paid only to 22 patients because the pharmaceutical companies concerned claimed that out of 438 patients, only 22 patients had died because of clinical trials and that the other deaths were unrelated and could have occurred due to various other reasons during clinical trials, such as the patients being already terminally ill or suffering side-effects of unrelated cause.

In the context of trials conducted by Swiss pharmaceutical companies, the committee reported seven deaths in 2010, none of which was compensated by Novartis Healthcare Pvt. Ltd. Further, a letter was sent to the company dated 20 April 2011 (F. NO.CT/SAE/2011-DCG (I)) by the Deputy Drug Controller (I) asking for the details of the compensation paid, other details of the site, etc. However, these reports and the responses from the Swiss pharmaceutical companies are not available in the public domain or on the website of CDSCO.

9.3. Calculating the Quantum of Compensation

However, deciding or assessing the quantum of compensation has raised many concerns in various quarters. In August 2012, MoHFW issued Draft Guidelines[45] for determining the quantum of compensation to be paid in the case of clinical trial-related injury or death. To assess compensation in the case of trial-related injury or death, the following parameters need to be taken into consideration:

1. age of the deceased;
2. income of the deceased;
3. seriousness and severity of the disease the subject was suffering from at the time of his/her participation in the trial; and
4. percentage of permanent disability.

The variation in the amounts can only be based on the seriousness of the illness or side-effect, and not on the age and income capacity of the clinical trial participant. Many CTPs are children, women, or people who are not earning. For such unemployed people, the

trial compensation may be nil or almost nil if it is based on workers' compensation. Given the widespread poverty in India, it is not surprising that people are willing to become clinical trial participants for a small amount of money, or for free treatment. In such a scenario, it is not appropriate to compensate victims based on their income or earning capacity. The compensation must be based on the income of the pharmaceutical industry or the sponsor who is bound to earn huge profits from the sale of the drug when it hits the market. Compensation should be based on the income level and on the profitability of the pharmaceutical company or the sponsor undertaking the trial and on the amount they spend on the R&D of the drug.

9.4. Insurance

The health care system in India today is highly privatized; a large majority of people access health care in the private sector and have to pay for it. 'Out-of-pocket' and catastrophic health care expenses are major factors responsible for the substantial percentage of Indians living below the poverty line. The public health care system is in a state of neglect due to reduced health budgets; it continues to provide services but in a limited manner. The number of people with insurance coverage is estimated at approximately 300 million (2010), and it is limited to state-initiated social health insurance available for those in the formal employment sector, through insurance schemes for the poor (largely the below poverty line [BPL] population) or through private insurance.

Sama's findings on the role of insurance and the policies of the sponsors on insurance and compensation are as follows.

According to KIs, generally, the sponsor takes out insurance coverage.

> *"The period of insurance is generally one year and the claim has to be made within 30 days of the expiry of the insurance to the company that has provided the insurance. While trials can cause adverse effects up to three to five years after the termination of trials, insurance does not cover post-trial issues. The insurance policy is worded in a manner that makes it clear that compensation would be paid only when the injury has been caused by the trial drug or when it can be directly attributed to participation in the trial. A linkage has to be established between the trial and the injury, and the responsibility for establishing such a link has been given to the PI and the EC, which are interested parties. As a result, to date, not a single injury has been linked to a drug trial."*

> *"Our lawyer on the EC is very particular about seeing to it that our centre and our trial are included in the insurance provided by the sponsor. If it is general insurance, then we usually go back to the sponsor and say, this much is not enough and that they need to specify that this site, with this PI, with these participants, will be covered by the insurance. The insurance is generally for the management of untoward adverse events or deaths that may occur during the trial".*

> *"Health insurance is a part of the consent process. Each trial participant is under health insurance coverage."*

Insurance is a contract, and all details or requirements of the contract need to be fulfilled to make a claim. Insurance is different from compensation, and the two should not be taken as one and the same.

As can be seen from the interviews, insurance for the limited period of the trial will not cover any post-trial medical problems that the clinical trial participants may face. It is a good thing that insurance covers injuries, side-effects, and other medical conditions or adverse effects that may occur during the trial. However, the hassles of making the claims to the insurance companies need to be highlighted, and the onus of obtaining the same should be placed on the sponsor, the funder, or the company, and not on the clinical trial participant.

It should be noted that although the clinical trial participant should have insurance coverage, paid by the sponsor or the pharmaceutical company, it cannot be counted as adequate compensation. The insurance company can pay the sponsor or the pharmaceutical company directly for any claims relating to the clinical trial participant. But the sponsor or the pharmaceutical company should pay the amount insured to the clinical trial participant immediately.

10

Post-Trial Access to Health Care

The Declaration of Helsinki contains a provision concerning the need for providing some benefits to research participants. Principle 30 states that "[a]t the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study" (World Medical Association [WMA] 1964, as amended in 2004, 2008).

Clearly, clinical trial participants should have PTA until the medicine is freely available in the public health care system. The issue of post-trial obligations needs to be raised, especially those associated with trials being conducted in developing countries like India by companies from developed countries. This should be stated clearly in the ICF. The sponsor should, prior to the granting of approval, make provisions for PTA in the informed consent form pertaining to a trial and undertake to ensure the best proven treatment at no cost to the participants.

10.1. Post-Trial Concerns of Interviewees

Sama's findings have been that almost all the participants interviewed expressed the view that the drug that had been tried on them should be made available to them even after the trial period. There was a great deal of anxiety among the participants throughout the trial period about having access to the drugs being tried on them. Some participants lamented that the trial drug was no longer available to them after the trial period.

> *"We are back to square one after the trial. I am not sure if I will be able to come back to the normal OPD and buy medicines. At least the trial drug had some impact on me. If I am put back on my old medicine, I may not get cured."*

> *"If I have no access to this drug in the post-trial period, what am I going to do? I might go back to the same treatment as before."*

> *"I feel this drug has helped me a lot. My itching has subsided and the patches have disappeared. It should be made available to me after the testing, because it works towards reducing the problems associated with the disease."*

Some participants said that the PI/doctor had informed them about the trial period and had made it clear that the drug would not be available post-trial, and that the participants would have to go back to the standard treatment.

> *"The study is now over. At the end of the trial, the doctor prescribed me medicines, referred me to a chemist shop, and requested them to give me tablets for the next six months for free, which, thankfully, they agreed to do."*

> *"The doctor told me that the injection would be provided only for one year until the end of the trial period. After that, in spite of having positive results from the injection, I could not get it any longer. My life has become restricted again."*

> *"The doctor told me very clearly that this drug is available only during the trial. Post-trial, I would need to go in for other treatment and buy my own medicines. The medicines are very expensive and I can't afford them."*

There is considerable expectation among the participants that the trial drug would be continued for some time, at least for one year after the trial period. Some felt that the trial drug was beneficial to them and argued that it should be made available free of cost to the trial patients.

Such expectations regarding PTA to the investigational drug seem reasonable, given the overall socio-economic context of the participants.

Was any treatment given to the clinical trial participants once the trial was over?

Many KIs were unable to respond to the question of access to the drug after the conclusion of the trial. They were not sure to what extent the sponsor should ensure that the CTP could have access to the investigational drug were it to prove effective.

> *"There is no post-trial access to drugs. Once the trial is over, drugs are not available to the subjects. Not even the standard drugs. They have to purchase them from the market. The new drugs may take two to three years to get their licence."*

> *"It all depends on the protocols. If the protocol says that we should continue providing this experimental drug for those patients who responded to the treatment, we will provide it. But generally the experimental drug is not provided post-trial to any patient."*

> *"If the drug is investigational, we prescribe some other drug since the trial drug is not available on the market. In Rajasthan, free treatment with generic drugs has become policy. The poor can get them free from the health centres. So it is not a big burden for the poor to access drugs in the post-trial period. However, I have my own concerns about the free-treatment policy. Most of the generics are almost branded. Some of them are manufactured by companies that are partly owned by politicians—all for profit."*

Interestingly, a KI said: "PTA for trial participants raises ethical concerns. PTA can be considered to be an inducement for patients to join clinical trials, essentially to get free/ subsidised access to the drug."

If PTA can be an inducement, can it not be an inducement when the trial is running or when the research team is recruiting participants?

As can be seen from the above interviews, it appears that PTA to health care services and proven medicines is rare. It is not included in the ICF and is not provided generally to the CTPs, even if the trial medicine has proven to be beneficial to them.

The term post-trial obligation describes the duty incumbent on the sponsors of the research study to provide a successfully tested drug to the research participants who took part in the relevant clinical trials, where there is a benefit to the patients and where they have no alternative treatment available to them, after conclusion of the trial. The obligation of providing PTA lies with the sponsor. Assuring PTA for the investigational product that is yet unlicensed would obviously require approval from the regulatory authority.

Company	Website link	What it says
Novartis	http://www.novartis.com/downloads/corporate-responsibility/resources/positions/clinical-trials-developing-markets.pdf	Clinical studies for innovative medicines and devices are only conducted in countries where there is reasonable expectation that the drug tested will be submitted for marketing authorisation and be made available to patients/ subjects, once proven safe and efficacious.
Roche	http://www.roche.com/clinical_trials.htm See the FAQ section	There are certain circumstances when, for the well-being of a patient participating in a trial, continued access to the Roche investigational medicinal product is necessary. Examples are serious, life-threatening or disabling diseases such as cancer or lupus, when no alternative treatment is commercially available. In these situations, following termination of the Roche Sponsored Clinical Trial, an adequate supply of treatment will be assured for all the Roche Sponsored Clinical Trial participants, until the Roche investigational medicinal product becomes available commercially.

However, issues surrounding PTA and obligation have become contentious topics, involving both 'principled' and 'practical' objections, such as the long time lag between research and licensing, the offering of undue inducement to CTPs, and the potentially 'prohibitive expense' of conducting clinical trials. Access to health care is an important issue to consider in research ethics, because an ethically appropriate clinical trial design requires an assessment of the level and the nature of care or treatment available outside the research context, as well as any possible future health benefits that might arise from the research.

Given the lack of affordable and accessible health care, it is not surprising that expenditure on health care is the second greatest cause of indebtedness in India. About 77 per cent of total health-related expenditure is out of pocket (OOP) in India.[46] Of this OOP, about 70

per cent is spent on drugs, followed by diagnostics and medical consultation. Thus, drug pricing is a critical area that needs to be considered within the realm of health research ethics. Similarly, in the context of PTA, there is a need to protect the safeguards provided by the Indian patents law and TRIPs, and also to protect the country's ability to produce essential drugs.

As Urmila Thatte et al. (2008) argue, "Medicines that are being evaluated in the Indian population must be made available to the population at an affordable price."[47]

10.2. Legal Provision of Post-Trial Access

In India, laws and guidelines are inconsistent, ambiguous, or silent about many aspects of PTA. There is no mention of PTA in the DCA. The only document that mentions PTA is the ICMR's Guidelines for Biomedical Research on Human Participants.

The section on PTA in the ICMR Guidelines refers to the Declaration of Helsinki (2000) about assuring PTA and the debate that followed. It then quotes the Declaration of Helsinki:

The lack or absence of rules that make post-trial follow-up mandatory allows sponsors to leave participants in a state of free fall. There is no accountability or responsibility for continuing to provide a helpful but unaffordable drug, for taking care of withdrawal symptoms, for remedying delayed negative repercussions, or for addressing the effects on the general health of the participants.

Post-Trial Access as described in the ICMR Guidelines

The Declaration of the WMA in 2004 reaffirmed "its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review." Therefore, whenever possible, the IEC should consider such an arrangement in the a priori agreement. Sometimes more than the benefit to the participant, the community may receive the benefit in an indirect way through an improvement in their living conditions; the establishment of counselling centres, clinics, and schools; and the provision of education on the importance of maintaining good health practices. For smaller-scale or student projects, providing post-trial benefits to the participants may not be feasible. Nevertheless, keeping in mind the importance of post-trial responsibility on the part of the sponsors or funders, conscious efforts should be made by the guides and by the institutions to initiate steps to continue to support and provide better care to the participants.

11

Conclusions and Recommendations

This chapter discusses and analyses the interviews and makes certain recommendations for action in the future.

Even within the limited purview of the exploratory study and the small sample size, the findings of the study clearly raise important issues for discussion, as well as significant concerns that constitute further areas of inquiry. While the findings further consolidate and inform an understanding of the conduct of clinical trials by the private sector, many interlinking issues also emerge. Further, the issues that emerge are mostly concerned with the legal and ethical issues that impinge on clinical trials that are conducted by various institutions and professionals: the informed consent-taking process; the assessment and award of compensation; the reporting of AEs, SAEs, and death; the issue of PTA; and the role of ECs and IRBs.

The research conducted by the Swiss pharmaceutical companies examined in this study is mainly focused on profit-oriented drugs, and none of the trials financed by the three companies in this study is concerned with neglected diseases. For instance, malaria, tuberculosis, and other diseases of the poor are not of research interest to them. The innovative preparations produced by these companies do not correspond to the pharmaceutical requirements in India for the treatment of neglected diseases. Further, the non-availability of innovative pharmaceuticals, particularly for the poor, has grave implications. In the case of drug resistance in current treatment, the newer and more effective preparations are not accessible to the poor.

11.1. Sourcing, Recruitment, and Motivation

The study revealed that in most cases, patients were recruited by PIs from their existing pool of participants through OPDs and IPDs on the premise that it was 'free treatment'. Most of the KIs interviewed indicated that the majority of CTPs belong to the lower social-economic class, have limited access to, or cannot afford, health care, and have an increased susceptibility to illness.

Sourcing and recruiting clinical trial participants through OPD, IPD, and health camps; inducing patients to enter into clinical trials by stating that it is 'free treatment' or that there is no other alternative; and claiming that no harm will result in trying a particular medicine. These practices are unethical and violative of the right to health and the right to life, as well as being violative of the autonomy of CTPs. Clinical trial participants should not be under any kind of undue influence. No misrepresentation should be made to them, such as statements claiming that the trial is treatment. CTPs should be volunteers, who agree to enter into the trial without facing any kind of coercion or influence.

This recruitment practice can lead to many problems, including conflict of interest; exploitation of the vulnerability of patients seeking health care; and exploitation of the unequal relationships between physician/investigator and patient/participant. Due to rampant poverty and lack of free medical facilities, participants opt for trials driven by desperation, as any treatment is better than no treatment.

While CTPs can be seen as the first to garner the advantages of a new medical procedure or development, they are also the first to subject themselves to the unknown repercussions or risks of an untested drug. This situation also raises concerns about the possibility of the subtle coercion of such patients to enrol in clinical trials.

It is well known that the doctor–patient relationship in India is unequal. Patients may not question the judgement or treatment or diagnosis of their doctor. They may be easily influenced by the doctor's advice. They may also believe that refusal to follow the doctor's advice to enter a trial would affect their access to care. Often the physician is the PI and the patient becomes a participant and treatment becomes an experiment. Patients often enter trials because they feel compelled to participate, for various reasons. Physician–investigators have conflicts of interest between their duty to their patients and their desire to seek the incentives that they receive to recruit CTPs. The information provided by the doctor seemed to significantly influence the decision of the patient to participate in a trial. The anxieties of the patient were allayed by the doctor's assurance that there would be no risk. The anthropologist Adriana Petryna describes the situation as the "creation of a patient consumer who buys into a particular idea of disease, who is educated by the trial recruiter about the best possible treatment, and who realises that he is unable to get that care outside of a trial."

Recommendations

1 PIs should not be allowed to include their own patients in clinical trials because of conflict-of-interest issues. The financial interests of doctors/physicians should be disclosed at the outset, and conflict-of-interest issues should be dealt with by the EC and the IRB.

2 Unless it is of specific therapeutic, diagnostic, or prophylactic benefits to them, those who are vulnerable or living in poverty, and those who are malnourished or ill, should fall under the exclusion criteria of the trial and should not be allowed to participate. The inclusion and exclusion criteria should be stated very clearly in the protocols, which

must include the factors of poverty and vulnerability. The justification for inclusion of vulnerable populations, such as tribals or persons of compromised autonomy, must be provided by the sponsors of the trial at the time of registration of the trial.[48]

3 In the event that a trial is conducted with tribals, persons with compromised autonomy, etc., then the sponsors need to show that the requisite standard of medical care (a full functioning primary, secondary, tertiary care system with road access) exists in the trial area to treat clinical trial participants in case of serious and not so serious adverse effects, emergencies, etc.[49]

11.2. Informed Consent and Role of the EC

Informed consent and information giving/taking are major issues that emerged from the findings of the study. Almost all the participants did not know the name of the drug that was being investigated or tested or the name of the company that was sponsoring the trial. All they knew was that they were participating in a trial.

When the prescribed conditions and guidelines are not followed, as can be seen from the interviews, the trial and the informed consent process are both vitiated and compromised. This could lead to an actionable wrong by doctors/physicians, investigators, sponsors, EC members, and IRB members. Hence caution should be exercised in recruiting clinical trial participants.

Whether medicines are distributed free of cost during a trial or during a post-trial activity or intervention in order to collect data, it is imperative that ethical principles are followed, that the participants' right to privacy and confidentiality is respected, that their free and informed consent has been taken, and that they have been informed about the aim and purpose for which the data are being collected. All data collected—whether pertaining to the clinical trial participants or to post-trial activities and interventions—should be anonymous, and high standards of privacy and confidentiality must be maintained by all those involved in the trial or data-collection process.

Informed consent, even if it does exist in certain cases, is not protection enough, because of the asymmetry in the knowledge possessed by the KI and the CTP. The information provided by the doctor seemed to significantly influence the decision of the patient to participate in a trial. The anxieties of the patient were allayed by the assurances given by the doctor that there would be no risk. The participant may not be adequately informed about the risks and/or benefits, nor may he/she have the means to demand compensation for any adverse health outcomes that may result from his/her participation in the trial. Obtaining consent from the CTP through the undue influence of the physician or doctor on the patient is not consent in the true sense, and amounts to breach of trust, and could further amount to negligence, battery, and assault.

The law with regard to informed consent is clear. The securing or giving of informed consent for participation in clinical trials must adhere to the provisions, both legally and ethically. Any breach of the provisions—such as the failure of the proposed CTP to have

read the form or understood the terms and conditions contained therein; the CTP being given no choice in the matter other than to sign the form; the CTP being told that no other treatment is available, and using this tactic to pressure the CTP to sign the form—would be tantamount to no consent having been given by the proposed CTP, and hence the trial would be completely illegal. Respect for patients and regard for their autonomy must be maintained at all times. The patient's rights cannot be violated. This is a legal requirement which is very often not followed. The fact that patients ask questions does not necessarily mean that they have given their informed consent.

CTPs should be made to understand that they have the right to withdraw from the trial at anytime. But it is also the duty and responsibility of the PI, the sponsor, etc. to withdraw the drug from trial the moment they receive evidence of adverse effects that are harmful to the CTPs. Details about the compensation to be paid by the sponsor through the PI or any such agency should be included in the ICF.

Recommendations

1 The securing of consent should be made a two-part process. In the first part, all the information required for giving/securing informed consent should be provided to the prospective participant, including details about the risks (probable, short-term, and long-term risks), benefits, side-effects, alternatives, treatment regime, etc. In the second part, steps should be taken to assess the prospective research participant's comprehension of the information delivered to her/him with an appropriate assessment tool. If the participant has understood the meaning and significance of the informed consent process, and then gives his/her consent willingly and voluntarily, only then should the process of informed written consent be regarded as such.

2 All the trial protocols including patient information sheet and consent forms should be approved by the Ethics Committee.

3 The clinical research team should be trained to explain the study's benefits and risks, and to ensure that the consent process is truly informed. Furthermore, often a third-party witness is required to be present during the informed consent process for non-literate participants.

4 The IRB and the EC should appoint a neutral person, who is not the PI, to play the role of a consent auditor who assesses the method or way in which informed consent is taken; the vulnerability of the clinical trial participant and the undue influence to which he/she may be subjected in order to secure his/her consent to participating in the trial; the decision-making capacity of minors and of mentally challenged patients/participants; and the administration of the informed consent process.

5 The PI should be made accountable for any violation of IC process; any violation will be dealt with penalty.

6 Copies of the patient information sheet and the signed consent form should be provided to the participants.

11.3. Reporting and Management of SAEs

Most of the participants were not informed in detail at the time of recruitment about the possible side effects and risks involved in participating in clinical trials. In a few cases, participants were instructed to report to the trial site in the event of any AE. PIs, on their part, maintained that the reporting of AEs is taken seriously, and that they strictly followed the letter of the law as per Schedule Y of the DCA.

Many times, KIs could very easily attribute the cause of death or the adverse reaction to natural causes or to the natural progression of the disease, as many of the CTPs enrolled are ill patients or severely ill patients who do not have any treatment available to them. It may not be obvious that the patients fared worse as CTPs than they would have in the absence of the research intervention. It can always be argued that the patient died of natural causes, and the same cannot be attributed to the action or inaction of the clinical trial. Such circumstances can make it extremely difficult for clinical trial participants or their family to obtain claims from the insurance companies. Indeed, it is difficult for them to even get compensation from the sponsor in case of severe impairment or death of the CTP, as the PI or the doctor–investigator would almost in all probability write "not attributable to the trial" in his/her report.

The PI generally plays a dual role as a researcher and a care giver, and receives monetary benefits from the sponsor for carrying out the trial(s). The trial design dictates/mandates the number of participants and it may well be that the PI gets paid according to the number of participants or is paid per participant who completes the trial. This has serious implications for the reporting of AEs as well as for the ability of participants to withdraw from the trial if they so desire. The PIs, given the circumstances, may prefer not to report the AEs, and instead may attempt to ensure that the participant continues to be part of the trial. The non-reporting of AEs to the sponsor or to any other relevant authority implies the existence of compromised data about the safety of the drug, and that its clearance for the market is based on false data about its safety, thereby raising concerns about the safety of the drug for users. The possible subsequent withdrawal of the drug from the market, due to concerns about safety, may affect the sponsors/pharmaceutical companies as well.

It is always difficult for the CTP or his/her family to prove that the deterioration in the health of the clinical trial participant, or the occurrence of an AE or SAE or death, was primarily due to the drug under trial. This is because the cause of an AE or SAE or death is assessed and recorded only by the PI, who may not want to record the true reason, as he/she has his/her own personal or professional or vested interest in the trial.

The fact is also that some pharmaceutical companies would want correct data/reporting, as otherwise it would be harmful to them in the long run.

It was also pointed out that the clinical investigator has a moral responsibility to report the AEs as he/she has the role of primary care giver to the patient. It is important that the CTPs be independently assessed by a doctor before the commencement of, and at regular intervals during, the trial. This could help CTPs gain an independent, unbiased opinion on the AE or SAE or the cause of death, and challenge the claims of the sponsor, or the

PI, or any other agency that may have conflict-of-interest issues and that may have other interests in the trial.

Recommendations

1 The CDSCO must ensure that pharmaceutical companies and CROs send prompt notification of all injuries or deaths in a trial, followed by the investigation findings and the action taken on these findings.

2 It must follow up on all reports to ensure that participants are provided immediate and long-term medical management and compensation is given for injury or death. Compensation details must be finalised before the start of any trial.

3 In cases of study-related injury, disability and death in human participants due to non-compliance with regulations or negligence, the law should hold the sponsor accountable and liable.

11.4. Post-Trial Access

Do the individuals who participated in the research study or clinical trial or experiment have any valid claims, legally or ethically, for continued access to the investigational drug? The provision of PTA is an important, yet complex and contentious issue, requiring further discussion. The study also demonstrated that there is no guarantee of PTA to the CTP. The drugs that are tested on the bodies of the CTPs will not be made available to them in times of sickness, but instead will be sold in markets to which they have no access.

India continues to be a preferred destination of Swiss pharmaceutical companies for clinical trials, primarily for drugs that are, paradoxically, out of the reach of a large majority in the country due to their high cost. This scenario, therefore, raises concerns about the conduct of trials on people who ultimately will not have access to the medicines that are being tested on them.

Thus, PTA, although largely ignored by companies, including Swiss pharmaceutical companies, is a critical issue in ensuring CTPs have access to medicines.

Recommendations

1 No trials should be approved by the CDSCO without obtaining the commitment of post-trial access from the sponsor.[50]

2 The drug tested in India MUST be marketed in India if proven to be successful; they ought to agree to a price control on the drug when it is marketed in India.

11.5. Compensation

There is an urgent need to appoint a permanent independent appellate body to arbitrate on issues related to trial injury/death and compensation. The new notification by the DCGI on compensation does provide for such a body. However, the problem is that further clarity is required on the proposed body's role and responsibility.

Further, cause of death or AE or SAE should be assessed independently by other doctors who are not related to the trial or to the sponsors, and compensation should be paid based on their report. All these factors should be placed on record and in the consent form prior to the commencement of the trial.

Moreover, the quantum of compensation for participation in human trials or experiments cannot and should not be based on the age of the participant, the income of the participant, the number of the participant's dependents, etc. Such calculations based on age, income earned, etc. are made under the Workmen's Compensation Act, 2009[51] in India. Under this act, a workman who is injured during the course of his work is given compensation calculated on the basis of the degree of his disability, his age, his salary, etc. Similarly, under the formula of the DCGI for calculating the quantum, the old get less compensation than the young; the better off get more compensation than the poorer. The same cannot be compared with or substituted for compensation to be given for AEs or SAEs or death during clinical trials. The measures for determining and awarding compensation in such cases have to be different.

Recommendations

1 In case of any injury occurring to the clinical trial participant, he or she shall be given free medical management as long as required.

2 In case of injury occurring to the clinical trial participant during the clinical trial, such participant shall also be entitled for financial compensation and the financial compensation will be over and above any expenses incurred on the medical management of the participant.

3 The expenses on medical management and financial compensation in the case of clinical trial injury or death of the clinical trial participant shall be borne by the sponsor of the clinical trial.

11.6. Insurance

The sponsor should take out insurance for all the clinical trial participants, and in the case of the settlement of any claims against the insurance companies, the sponsor should pay the participants up front and reclaim the amount from the insurance companies at its own cost. The clinical trial participants should not be made to pursue insurance companies and forced to file cases against them for refusing to pay the claims. It is well known that insurance companies are profit-making organisations who find loopholes in contract

clauses to avoid paying the insured amount. The sponsor may have to fight to settle its claims against the insurance companies, but it should pay the amount insured and the compensation up front to the clinical trial participant or to his/her family.

Recommendations

1 Companies should be required to provide comprehensive health insurance for all clinical trial participants to take care of all health needs, including ancillary care.

2 The sponsor or the pharmaceutical company should pay the CTP and reclaim the sum from the insurance company at its own cost and through its own lawyers. The CTP should not be expected to make claims against the insurance companies, as this would only add to his/her worry and stress.

11.7. General Recommendations

1 Regulation is necessary at all levels of this network – the drug company, the CRO, the institution conducting the trial and the individual researchers – to ensure that drug trials are conducted in compliance with the ICMR's ethical guidelines in addition to guidelines of GCP.

2 Clinical trials are conducted by CROs, which develop the infrastructure for trials by identifying and establishing trial sites, such as places in small towns and private hospitals, and compiling databases of potential clinical trial participants. In India, Schedule Y of the DCA does not even take cognizance of CROs, let alone lay out clauses for their regulation.

3 There is an urgent need to develop and strengthen mechanisms for the legal regulation of clinical trials and CROs, as well as for determining the liability of clinical trial participants and of those in charge, including the EC.

4 ECs must be registered, accredited, and made accountable and liable for their decisions. EC members must be trained, and it needs to be ensured that ECs have the capacity, resources and independence to review and monitor drug trials.

5 The EC, the IRB, sponsors, funders, companies, investigators, etc. should all be made liable for any legal or ethical issues, or for any violations that occur during the trial. The protocols should be followed strictly.

Annex I

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Annex II

Participants' Profiles

Code	Age/ Gender	Education	Caste/ Religion	Work Profile	Marital Status	Income/ Assets	Family members relevant
CTP-1	75 / M	Graduate	Hindu	Retired now; earlier advocate's clerk	Married	Stays in rented house; dependent financially on daughters (married and live separately)	Wife; four daughters
CTP-2	63 / M	Graduate	Kshat-riya / Hindu	Railway catering business	Married	721.76 USD per month; own house; owns a T.V., fridge, car	Family
CTP-3	60 / M	7th Class	Muslim	Auto-rickshaw driver earlier; now helps at his son's tea stall	Married	25 USD per month	3 sons (live separately; he lives on his own)
CTP-4	64 / F	Graduate	Parsi	Retired; earlier worked in a Bank	Married (husband died)	Own house	Daughter (lives separately)
CTP-5	47 / F	10th Class	Jain	Housewife; husband works in a bank	Married	902.20 USD monthly income	Husband, 2 sons and their respective families
CTP-6	47 / M	11th Class	Rajput / Hindu	Chief operator at a marble processing unit	Married	333.36 USD – 416.70 USD monthly income; own house	Wife, two children, his younger brother and his late elder brother's wife and children

CTP-7	65 / M	9th Class	Maratha / Hindu	Farmer	Separated (wife left him 30 years ago with daughter)	5-6 acres of land in the village; 50% royalty of the earnings from the farm; two rooms in family home	Brothers (having family dispute with them)
CTP-8	36 / M	9th Class	Scheduled Caste / Hindu	Butcher; agent for sale of livestock to other butchers	Married	Rented house	Parents, his brother, his wife and his 3 children
CTP-9	47 / M	10th Class	Maratha / Hindu	Mechanic with state roadways; farmer	Married	Own house; plot of land of around 2.5 hectares and a bore well	Parents, wife, two sons and his brother's family
CTP-10	25 / M	Engineering	NA*	Student (completed engineering, pursuing short term courses in networking)	Unmarried	Own house and has three two wheelers and one four wheeler	Father, mother, two older sisters
CTP-11	39 / M	5th Class	Base / Hindu	Runs a small grocery shop outside his home	Married	133.34 USD – 166.68 USD per month	Joint family with his mother, wife and two children
CTP-12	56 / M	Not literate	Brahmin/ Hindu	Farmer; receives money from renting his car commercially	Married	A two wheeler and a car, car used as a taxi; 250.02 USD– 333.36 USD per month	Wife, 5 sons

Code	Age/ Gender	Education	Caste/ Religion	Work Profile	Marital Status	Income/ Assets	Family members relevant
CTP-13	49 / M	Not literate	NA	Farmer; work under the Mahatma Gandhi National Employment Scheme	Married	90.22 USD - 108.26 USD per month; TV	Joint family
CTP-14	35 / M	Graduate+ diploma in education	Dalit / Christian	Teacher	Married	126.21USD/ monthly; two-room house; has a fridge, TV and a two-wheeler (only earning member)	Joint family
CTP-15	40 / F	10th Class	Muslim	Housewife	Single (never married)	NA	Sister; sister's family
CTP-16	30 / F	9th Class	Muslim	Housewife; husband owns a grocery store	Married	Rented house; television and a Luna TVS (two wheeler)	Husband and child
CTP-17	38 / F	NA	Hindu	Stitching work	Single/ Separated	NA	Sister; 2 children

* NA - Not Available

Annex III

Informed Consent: Appendix V - The Drugs and Cosmetics (Third Amendment) Rules, 2013

1. Checklist for study subject's informed consent documents-

1.1. Essential Elements

1. Statement that the study involves research and explanation of the purpose of the research
2. Expected duration of the subject's participation
3. Description of the procedures to be followed, including all invasive procedure.
4. Description of any reasonably foreseeable risks or discomforts to the subject
5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.
6. Disclosure of specific appropriate alternative procedures or therapies available to the subject.
7. Statement describing the extent to which confidentiality of records identifying the subject will be maintained and who will have access to subject's medical records
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomised trials).
9. Statement describing the financial compensation and medical management as under:-
   (a) In the event of an injury occurring to the clinical trial subject, such subject shall be provided free medical management as long as required.
   (b) In the event of a trial related injury or death, the sponsor or his representative, whosoever has obtained permission from the licensing authority for conduct of the clinical trial shall provide financial compensation for the injury or death.
10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11. The anticipated prorated payment, if any, to the subject for participating in the trial.
12. Subject's responsibilities on participation in the trial.
13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled.
14. Any other pertinent information.

1.2 Additional elements, which may be required

(a) Statement of foreseeable circumstances under which the subject's participation may be terminated by the investigator without the subject's consent.

(b) Additional costs to the subject that may result from participation in the study.

(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by subject.

(d) Statement that the Subject or Subject's representative will be notified in a timely manner if

significant new findings develop during the course of the research which may affect the subject's willingness to continue participation will be provided.

(e) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.

(f) Approximate number of subjects enrolled in the study

2. Format of informed consent form for subjects participating in a clinical trial-

Informed Consent form to participate in a clinical trial

Study Title:	Study Number:
Subject' Initials:	Subject's Name:
Date of Birth / Age:	Annual Income of the subject:
Address of the subject:	Qualification:

Occupation: Student/Self-Employed/Service/Housewife/Others (Please tick appropriate)

Name and address of the nominee(s) and his relation to the Subject.....…..(for the purpose of compensation in case of trial related death).

Please initial Box (subject)

(i) I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

Signatory's Name:	Date:
Signature of the Investigator:	Date:
Study Investigator's Name:	Date:
Signature of the Witness:	Date:
Name of the Witness:	Date:

(Copy of the Patient Information Sheet and duly filled informed Consent Form shall be handed over to subject or his/her attendant.)

Source: *The Drugs and Cosmetics (Third Amendment) Rules, 2013*

Annex IV

Sama's Work on Clinical Trials in India

Sama–Resource Group for Women and Health[52] is a Delhi-based organisation that was established in 1998 by a group of feminist health activists from the autonomous women's movement with a background in public health care. Sama advances an understanding of health from a gender, caste, class, and rights perspective, and seeks to locate the concerns of women's health in the context of contemporary socio-historical, economic, and political realities.

Sama's work in the field of medical research in India began with its engagement in the campaign against unethically tested and invasive hormonal contraceptives and the anti-fertility vaccine. Sama members were involved in the campaign against the violation of the rights of women participants in the natural history study on the progression of cervical cancer, conducted at the Institute of Cytology and Preventive Oncology (ICPO)–Indian Council of Medical Research (ICMR), and that came to light in the mid-1990s.[53]

In mid-2009, the Human Papillomavirus (HPV) vaccine "demonstration projects" were conducted by the Program for Appropriate Technology in Health (PATH), a Seattle-based non-governmental organisation, in collaboration with the Indian Council of Medical Research (ICMR) and the state governments of Andhra Pradesh and Gujarat. The projects were funded by the Bill and Melinda Gates Foundation. The vaccines used, Gardasil and Cervarix, were donated to PATH by the manufacturing companies; in this case, GlaxoSmithKline and Merck Sharp and Dohme (MSD). These HPV vaccines were administered to approximately 23,000 young girls, of between 10 and 14 years of age, in the district of Khammam in Andhra Pradesh, and in the district of Vadodara in Gujarat. In March 2010, Sama carried out an investigation[54] into a Human Papilloma Virus (HPV) vaccine study conducted in Andhra Pradesh. The Sama team found that there were many irregularities in the process of obtaining informed consent, in the reporting of AEs, and in the protection afforded to the study participants in the event of an AE. They found that the deaths of four young girls after the study were improperly investigated. The Sama investigation contributed to the setting up of a government-appointed inquiry committee that confirmed the findings of the Sama team. In April 2010, the Ministry of Health and Family Welfare (MoHFW) suspended the study.

In addition, Sama has been actively involved in the National Bioethics Conferences (NBC) [55]and was the co-organiser of the 4th NBC in Delhi in 2010. In 2011, Sama co-organised a National Consultation on the Regulation of Drug Trials in New Delhi.[56] It was attended by nearly 60 participants, who mainly comprised representatives from activist health networks, the medical and scientific community, the media, and women's groups, as well as legal experts and policy makers. Both the broader context of clinical trials as well as specific case studies of trial malpractice were explored. In 2012–13, Sama conducted a qualitative study on the experiences of participants of clinical trials in India. The data-collection phase has been completed and analysis is underway.[57] Sama plans to introduce the findings of the study at various levels of the system that governs the biomedical research enterprise in India.

Sama has consistently raised the legal and ethical issues involved in clinical trials conducted by various institutions and professionals, the role of the Ethics Committee (EC) and the Institutional Review Board (IRB), the issue of informed consent (IC), the reporting of adverse events (AEs) and serious adverse events (SAEs), and the matter of compensation through discussions with, and recommendations to, the MoHFW.

In 2012, Sama was approached to undertake an exploratory study on clinical trials conducted by Swiss pharmaceutical companies in India by the Berne Declaration (BD), an independent Swiss NGO with more than 22,000 members (BD, www.evb.ch/en). The main aim of the study was "to document the conduct of clinical trials sponsored by Swiss pharmaceutical companies in India and to verify if they comply with the relevant ethical standards and the regulatory environment in India."

End Notes

[1] Kulkarni, K., and Mohanty, S. (2013). 'Novartis loses landmark India patent case on Glivec'. *Reuters.*[http://in.reuters.com/article/2013/04/01/india-drugs-patent-novartis-glivec-idINDEE93000920130401], accessed 2 April 2013.

[2] PricewaterhouseCoopers. (2010). *Global Pharma Looks to India: Prospects for Growth* [http://www.pwc.com/gx/en/pharma-life-sciences/publications/india-growth.jhtml], accessed 12 April 2013.

[3] Ibid.

[4] Schedule Y, (amended version 2005), *Drugs and Cosmetics Act 1945,* Central Drugs Standard Control Organisation, India; [http://cdsco.nic.in/html/schedule-y%20(amended%20version-2005)%20original.htm], accessed 23 March 2013.

[5] World Health Organisation, International Clinical Trials Registry Platform, [http://apps.who.int/trialsearch/default.aspx.], accessed 14 June 2013.

[6] Raju,A. (4 May 2013). Clinical trials industry witnessing downtrend in India: Dr C Raghu. *Pharmabiz,* [http://pharmabiz.com/ArticleDetails.aspx?aid=75161&sid=1], accessed 16 June 2013.

[7] A CRO is an organisation/person that is contracted by a sponsor to manage the various steps in the drug-development process, including the conducting of preclinical studies, clinical study design and execution, data management, analysis, medical writing, and regulatory submission. Ref: Tufts Center for the Study of Drug Development. "Tufts CSDD Outlook 2010" [http://csdd.tufts.edu/_documents/www/Outlook2010.pdf], accessed 30 December 2010.

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[9] Cygnus Research. (September 2011). *Industry Insight, Clinical Trials in India.* Summary. [http://www.researchandmarkets.com/reports/2017844/industry_insight_clinical_trials_in_india], accessed 23 May 2013.

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[11] Département Fédéral des Affaires Etrangères. (2012). *Annual Economic Report 2011–2012.* New Delhi. [http://www.switzerland-ge.com/de/filefield-private/files/559/field_blog_public_files/11432], accessed 12 April 2013.

[12] Ibid.

[13] Op.cit.

[14] See [http://www.booz.com/global/home/what-we-think/global-innovation-1000/top-innovators-spenders].

[15] See [http://www.moneycontrol.com/stocks/marketinfo/netprofit.php?optex=BSE&opttopic=&group=A&indcode=All], accessed 10 April 2013.

[16] Rajagopal, D. (17 June 2013). 'Novartis sales team involved in bribing the stock market for over a year.' *The Economic Times,* [http://m.economictimes.com/news/news-by-industry/healthcare/biotech/pharmaceuticals/novartis-sales-team-involved-in-bribing-stockists-for-over-a-year/articleshow/20622629.cms], accessed 19 June 2013.

[17] Kulkarni, K., and Mohanty, S. (2013). 'Novartis loses landmark India patent case on Glivec'. *Reuters.*[http://in.reuters.com/article/2013/04/01/india-drugs-patent-novartis-glivec-idINDEE93000920130401], accessed 2 April 2013.

[18] Business Standard (14 May 2013), 'Court dismisses Roche's patent petition against Intas' [http://www.business-standard.com/article/companies/court-dismisses-roche-s-patent-petition-against-intas-113051401020_1.html], accessed 15 June 2013.

[19] Campaign for affordable Trastuzumab (16 August 2013), 'Roche relinquishes Trastuzumab patent in India' [http://donttradeourlivesaway.wordpress.com/category/campaign-for-affordable-trastuzumab/].

[20] Ibid.

[21] Op.cit.

[22] Supreme Court of India (Civil Original Jurisdiction), I. A. No. of 2012, 'Swasthya Adhikar Manch, Indore versus Ministry of Health and Family Welfare'.

[23] See [http://164.100.47.5/newcommittee/reports/englishcommittees/committee%20on%20health%20and%20family%20welfare/59.pdf].

[24] The work done by Parliament is not only varied in nature, but considerable in volume. As it has limited time at its disposal, it cannot give close consideration to all legislative and other matters. A good deal of its business is, therefore, transacted by what are called Parliamentary Committees.

[25] Sixty-sixth report / CDSCO, April 2013.

[26] See [http://cdsco.nic.in/html/copy%20of%201.%20d&cact121.pdf].

[27] See[http://icmr.nic.in/ethical_guidelines.pdf].

[28] See [www.mciindia.org/Acts andAmendments/TheMedicalCouncilAct1956.aspx], [http://www.ccimindia.org/cc_act_1970.html].

[29] See [http://cdsco.nic.in/html/GCP.htm].

[30] Clinical Trial Participants (CTPs) are those who undergo the clinical trial.

[31] The Key Informants (KIs) in this study are Principal Investigators (PIs) and Clinical Research Coordinators (CRCs). The CRCs are recruited by the hospitals or institutes, and may or may not be staff. They are hired to coordinate the clinical trial along with the PIs.

[32] There is no official definition of the roles and responsibilities of a CRC in Schedule Y and ICH-GCP makes no mention of CRCs. CRCs do all the documentation work, mediate between PIs, patients, clinical trial participants (CTPs) and other players.

[33] www.clinicaltrials.gov.

[34] www.ctri.nic.in.

[35] The multi-site research Participants' Perspectives in Clinical Trials was carried out to gain insights into the experiences of participants in clinical trials across public as well as private health care institutions. The field work was carried out in the states of Delhi, Gujarat, Maharashtra and Andhra Pradesh during 2012-2013.

[36] According to the Guidelines for BA/BE studies by CDSCO (2005), Bioavailability can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolic concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the early drug development can serve as a benchmark for subsequent BE studies.

Bioequivalence studies should be conducted for the comparison of two medical products containing the same active substances. The studies should provide an objective means of critically assessing the possibility of using them interchangeably. Two products marketed under different licences, containing the same active ingredient, must be shown to be therapeutically equivalent to one another in order to be considered interchangeable.

[37] CTPs are often referred to as subjects, research subjects, and trial participants by KIs.

[38] Huijstee, V. M., and Schipper, I. (2011). Putting Contract Research Organisations on the Radar: An exploratory study on the outsourcing of clinical trials by pharmaceutical companies to contract research organisations in non-traditional trial regions. Amsterdam, Dutch Ministry of Foreign Affairs, ISBN 978-90-71284-68-7, Published by Stichting Onderzoek Multinationale Ondernemingen (Centre for Research on Multinational Corporations) [http://somo.nl/publications-en/Publication_3615/at_download/fullfile], accessed 10 February 2013.

[39] More information on the notification is available on the CDSCO website. See [http://www.cdsco.nic.in/].

[40] Report prepared by the US *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.* Published in 1979, it puts forward three ethical principles for the protection of human subjects of research – respect for persons, beneficence and justice. See http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html.

[41] CDSCO. (2011). *CDSCO draft guidance for industry on reporting serious adverse events in clinical trials,* [http://www.cdsco.nic.in/SAE%20GUIDELINES%2005-05-2011.pdf], accessed 25 January 2013.

[42] More information on the notification is available on the CDSCO website. See [http://www.cdsco.nic.in/]

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[45] Guidelines for determining quantum of financial compensation to be paid in case of clinical trial related injury or death, date: 03.08.2012, MoHFW.

[46] Prayas, (2011), Out of Pocket Expenditure in Health Care, Report of the study in Five States of India.

[47] Thatte, U.M., and Bavdekar, S. B. (2008), *Clinical Research in India: Great Expectations?,* Journal Postgraduate Med, No. 4, pp. 318–323 [http://www.jpgmonline.com], accessed 3 April 2013.

[48] Locost, Sama and Dr Amar Jesani, Recommendations to the Expert Committee constituted by MOHFW to formulate policy. Guidelines, SOPs for approval of new drugs and clinical trials 2013.

[49] Ibid.

[50] Op-cit.

[51] See the website of the Ministry of Labour and Employment [http://labour.nic.in/content/innerpage/contact-us.php].

[52] See www.samawomenshealth.org for more information.

[53] Sarojini N., *Forthcoming publication.* When no lessons are learnt: The continuing saga of unethical research on poor women.

[54] Sarojini N., Anjali S., and Ashalata S. (2010). Findings from a Visit to Bhadrachalam: HPV Vaccine 'Demonstration Project' Site in Andhra Pradesh, 27–30 March 2010, Sama.

[55] See http://nbcijme.ijme.in/.

[56] Sama–Resource Group for Women and Health. (2012). *Report of the National Consultation on Regulation of Drug Trials* (September 2011), Sama.

[57] Sama–Resource Group for Women and Health. (2012-13). *Action Research on Participants Perspectives on Clinical Trials,* Forthcoming publication.

Sama is a Delhi-based non governmental organisation working on issues of women's health and rights. Sama seeks to locate the concerns of women's health in the context of socio-historical, economic and political realities, and find linkages between women's well-being and livelihoods, food, violence and other larger issues that affect their lives. Sama's core work areas include issues related to Public Health, Reproductive and Medical Technologies, Ethics and Regulations of Clinical Trials and Violence Against Women. Sama engages with a range of organisations, health networks, people's health movement, policy makers and academia through strategies of policy monitoring and advocacy, capacity building, research, knowledge creation and dissemination.

Founded in 1968, the Berne Declaration (BD) is an independent Swiss non-governmental organisation formed to combat the root causes of poverty by promoting more equitable and sustainable relations between Switzerland and the developing world. As a not-for-profit organisation with 23 500 members, the BD is committed to global justice and addresses issues of trade policy, commodity production and trade, the politics of food, finance, fair trade and health. As part of a worldwide network of human rights groups, environmental and development organisations, the BD promotes a more equitable and humane route to global development. To this end, the BD carries out investigative research, runs public campaigns to raise awareness and undertakes successful advocacy work in Switzerland and on the international stage.